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Mathison Memorial Lectures.[1]

VIROLOGY AS AN INDEPENDENT SCIENCE.

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LECTURE I: THE FOUNDATIONS OF VIROLOGY.

NEARLY forty years ago Gordon Clunes Mathison was killed on Gallipoli, and today I have been honoured by the invitation to pay tribute to his memory in these Mathison memorial lectures. Time moves steadily on its course, and with the years a memorial lecture like this must inevitably lose something of its character as a personal tribute to the memory of the man it honours. I think that I am the first Mathison lecturer whose knowledge of Mathison comes wholly from what other men have said or written about him. To me he has always been one of those "inheritors of unfulfilled renown" who, with Rupert Brooke, Moseley and many another marked for greatness, fell in the first World War. But I have no memory of him to offer you. I can only speak at second hand of that vitality and charm, the enthusiasm that reached out toward the new scientific medicine that was dawning in 1914, and the quick grasp of all knowledge that was relevant to his profession—the things that impelled those who knew him to found these lectures. But in one sense I have a closer association with Mathison than anyone else. Before he left on active service Mathison had been appointed director of the clinical laboratories at the Melbourne Hospital, and there is no doubt that had he survived the war he would have been the first director of the Walter and Eliza Hall Institute. In a sense, therefore, I am his successor in that post, and that must be some justification for my choice of a subject, for I wish to speak about a phase in the development of medical science which on the one hand has been a major influence on the work of the institute ever since 1923, when I first joined the staff, and on the other has been significantly influenced by the work of the institute.

There is now a well-developed science of virology, which at the present time is probably exerting more influence than any other biological science on the really basic aspects of biology. When Mathison fell in 1915 there was no vestige of such a science. I can remember well how in my day as a medical student there were two phrases wrapped about with an aura of power and mystery, "the ductless glands" and "the filterable viruses". They were entities which, though indubitably important, did not seem to fit into the pattern of the rest of what we were taught in physiology and bacteriology. There was one other set of facts which, although I do not think we realized it at

[1] Delivered on October 7 and 9, 1953, at the University of Melbourne.

the time, also failed to fit in in any way with the rest of biology—those concerned with antibodies, antitoxins, agglutinins and the like. The most gratifying experience of my thirty years as a professional research worker in microbiology has been to have, as it were, a seat in the front row, to watch how immunology and virology have grown to their present status as integral parts of the structure of the biological sciences. Tonight I will try to give you my picture of how virology grew to maturity within the last thirty years.

Perhaps there is one point I should make before I start. When I speak of the science of virology, I am concerned primarily with the structure of relatively academic research, discussion and speculation that has provided a basis for thought about the practical and theoretical problems of virus disease. But like every other science, and perhaps to a greater degree than most, the study of viruses developed out of intensely practical considerations. The prevention and cure of disease, especially of serious epidemic diseases like yellow fever or small-pox, has always been regarded as of urgent importance, and success in such efforts as something most worthy of acclaim. The first problem of virus disease to be tackled at the scientific level was the prevention of small-pox. The second was Pasteur's attempt to understand the nature of rabies and to find means of preventing the onset of symptoms and death after the bite of a rabid dog. Today the most important practical task is to develop methods of immunization against poliomyelitis.

These urgent practical problems have determined to a very large extent the fields in which microbiologists have worked. But when practical matters are being studied, fundamental knowledge always advances. Pasteur devised a practical method of treating persons bitten by rabid dogs; but to this day no one is quite certain whether it is or is not a life-saving measure. Yet in the course of that work Pasteur discovered the basic phenomenon of the attenuation of a virus by continued growth in some other species of animal. This was of vastly more importance, both theoretical and practical, than the dubious empiricism of the Pasteurian treatment of rabies—and in recent years has actually led to the development of highly efficient means of prophylaxis against rabies in dogs. A more recent example from my own experience is in regard to influenza virus. With the experience of 1918-1919 behind us, most of us felt in 1939 that one of the most urgent wartime jobs was to develop means of immunization against influenza. By the end of the war the whole experimental approach to influenza had been changed and the way was open for spectacular theoretical advances of the most fundamental character.

Probably most of the fundamental concepts of virology have arisen in the first place from investigations made primarily and wholeheartedly to control infectious disease. This is perhaps its greatest fascination as a field in which to work. Nowadays the opportunity to make major practical advances is much more limited than in the past; but there is always the feeling that any of the academic studies which come to fruition may contain the germ of something that may in the long run be of benefit to human medicine. But I would remind you again that in speaking of the foundations and the substance of virology I am regarding it as a science, not as a branch of practical medicine.

There is one human disease whose history runs like a central theme through the whole development of virology—small-pox. The story begins in the eighteenth century, when small-pox had become completely endemic in the great cities of Europe as the major cause of mortality in children, and as the outstanding peril that any young man coming from the country to seek his fortune had to face. In many ways small-pox, by its very nature, is a disease that is unusually easy to understand, and in the eighteenth century the essence of the situation was as clear as it is today. The lesions of the disease are highly characteristic and dramatically repulsive—when severe small-pox is current there is rarely any doubt about the diagnosis. Patients also become infectious for others just about the time when the rash first appears, and this would ensure that the twelve-day incubation period would be recognized very early in the history of small-pox. It would also be natural to believe that the disgusting-looking "matter" in the pustules was or contained the agent of the disease, and when Lady Mary Wortley Montague brought "variolation" back from the east and popularized it in England as a preventive against the small-pox, it was possible to prove this by inoculation of the "matter" to the skin of a susceptible child. Moreover, small-pox left its mark; the pitted face was an always visible reminder of past infection, and no one could escape from recognizing in every fresh epidemic of the disease that those who had been marked in the past were spared. The fact that one attack of small-pox conferred a lasting immunity was indubitable.

By the time of Jenner, knowledge of small-pox was more advanced and more accurate than the knowledge of any other infectious disease. The features to be stressed are the following: (i) the specific nature of small-pox as a disease easily distinguishable from any other, both by its symptoms and by the limitation of immunity to those who had previously suffered from such symptoms; (ii) the clear evidence of its natural transmission from early case to susceptible child with a relatively constant incubation period; (iii) experimental transmission with diseased material from the local lesions by inoculation into susceptible hosts. These three features provide a basis for all subsequent work on virus disease of man and the mammals generally. The transmission of infection by the inoculation of diseased tissue into a normal animal is a straightforward, easily understood type of experimental approach. It is also one full of potential fallacies, as witness John Hunter's famous experiment from which he concluded that syphilis and gonorrhœa were two manifestations of the same disease.

It was a tremendous advance when Koch freed experimenters from the necessity of using crude tissue extracts and the like for the transfer of bacterial disease, by showing how pure cultures of bacteria could be isolated, grown apart from any living tissue and then shown to be capable of inducing disease in experimental animals. These methods allowed a much more sophisticated and effective approach to many infectious diseases. For a time in the 1880's it seemed as if only effort and more refined methods were needed to ensure the isolation and cultivation of all the agents of infectious disease. But many types of infection continued to resist this approach—disease could be transferred only by the use of infected tissues or fluids. Improving microscopic techniques failed to disclose any characteristic parasite. Then in 1888 it was discovered by Beijerinck that the agent of a plant disease, mosaic of tobacco, could pass through the pores of a porcelain filter impervious to bacteria. This demonstration that an agent of disease could exist as an apparently unorganized soluble substance—a *contagium vivum fluidum*—made a stir in scientific circles at the time; but from our point of view the finding ten years later by Löffler and Frosch that foot and mouth disease could also be transmitted by filtrates was more important. This was the first instance in which the filterability of the agent of an animal disease had been demonstrated. Gradually, by steps that I need not detail, the concept of the filterable virus developed. Gradually it began to be realized that of the three main characteristics of such agents—invisibility under the microscope, capacity to pass a bacteria-proof filter and inability to grow on bacteriological media—the last was the most important and could be better expressed in the phrase "multiplying only within living tissues of a susceptible animal". In time it emerged that there were tiny parasites which, although equally confined to multiplication in appropriate living tissues, could be seen microscopically if heavily stained and were by no means as easy to pass through filters as, say, foot and mouth virus. The virus in vaccine lymph was a good example. About 1930 the term "filterable" was gradually dropped and biologists generally had adopted the concept that there was a class of pathogenic agents much smaller than bacteria which could grow only on living cells, and for which the name "virus" was appropriate.

Even before this period bacteriologists had developed excellent technical methods, and they had no difficulty in

seeing how virus diseases should be handled in the laboratory. In general the procedure envisaged was to pass infective material through a filter to get rid of bacteria and then to "culture" the material in an animal susceptible to the pathogenic agent. If the amount of virus was to be estimated, then dilutions must be prepared and each dilution inoculated into one or more susceptible animals till a point was reached when disease was no longer produced.

The practical difficulty was simply the expense of using very large numbers of cattle for foot and mouth disease or of monkeys for poliomyelitis. To do what a single agar plate will do for an estimation, say, of the number of staphylococci in a cubic centimetre of blood would require at least a dozen monkeys for a comparable titration of material containing poliomyelitis virus. The first major technical development in virus research was the use of small laboratory animals for quantitative experimental studies. It was not necessary that the animal should show the symptoms characteristic of the natural disease. All that was needed was that the virus should both multiply in the animal and show by some unequivocal symptom or lesion that it had multiplied. The first development of quantitative work of this sort was for the study of foot and mouth disease. Guinea-pigs were used, and the virus was inoculated into the pad of the foot, where it produced a typical vesicle.

The Mouse as Experimental Animal.

Then about 1930 it was found that rabies virus multiplied just as readily in the mouse's brain as in the brain of the dog or rabbit. Very soon intracerebral inoculation in mice three to five weeks old became the standard method for the study of many viruses responsible for disease of nervous tissues, and later on for a number of viruses without any obvious natural predilection for such tissues. This was an important development for several reasons. In the first place it brought into prominence the fact that if an infective agent was placed in some sheltered tissue not normally exposed to infection, it might grow more freely and produce signs of illness and death which would not result if "ordinary" methods were used. Secondly, it was a method that allowed the use of adequate numbers of experimental units. To rear a mouse to three to four weeks costs only about as much as a tube of bacteriological medium, and any investigator with a good mouse-breeding unit behind him has the tools needed for effective quantitative experimentation.

Thirdly, it made it possible to use reasonably accurate methods for detecting antibody against the virus being used. The principle of most methods was to find the smallest amount of virus that would kill half the mice into which it was inoculated and to take, say, 100 times this amount of virus as a standard dose. If that dose was mixed with immune serum and inoculated into mice they would survive; with normal serum they would die.

Perhaps the best way of indicating how such quantitative methods based on the intracerebral inoculation of mice could be applied to a major problem in preventive medicine will be to tell something of the story of yellow fever research.

There were three phases in the conquest of yellow fever. The first covered the investigations of the United States Army Commission in Cuba under Walter Reed. The casualties from yellow fever in the Spanish-American war and the growing popularity of the theory of Carlos Finlay that yellow fever might be spread by the mosquito combined to stimulate the inquiry. Human volunteers were the experimental animals. The hypothesis of mosquito spread was soon proved correct. Yellow fever was carried by the mosquito now called *Aëdes ægypti*, which was infected by feeding on human patients during the few days when the virus circulates in high concentration in the blood. The infected mosquito could transmit yellow fever only after a period of seven to twenty days had elapsed since its feed on infective blood—the extrinsic incubation period. Without any real knowledge of the nature of the pathogen—which at that time might have been protozoon, spirochæte, bacillus or virus—this provided the basic information that was to make it possible for Gorgas to eliminate yellow fever from Cuba and the canal zone within ten years. Rid a city of *Aëdes ægypti* and there will be no more yellow fever.

The second stage followed from the demonstration by Stokes Bauer and Hudson, in 1928, that rhesus monkeys were highly susceptible to yellow fever, coming down with much the same symptoms as stricken humans. Filtration experiments made it abundantly clear that a virus was concerned. The virus could be obtained in very high concentration in monkey blood or liver, and could be stored and used in any type of experiment that was desired. This opened the way for the third phase, the adaptation of the virus to growth in the mouse brain. Once mouse adaptation had been achieved, experiments and routine tests could be multiplied indefinitely. In particular it allowed the first great serological surveys to be made. It is axiomatic that you will never understand a disease until you can identify not only the typical case, but also the often much more numerous subclinical infections. The only practical way to do this is to use the serological survey. In the early 1930's it was of the first importance to know in what areas of Africa yellow fever was endemic in jungle animals (monkeys and the like) and the jungle mosquitoes. The most practical approach was to take native communities at various parts of Africa and obtain serum from a cross-section of the population covering all ages, but particularly children. Each serum was tested by inoculating a standard mixture of serum and virus into each of six mice intracerebrally. If all mice survived, the serum contained antibody and the person from whom it was drawn must have been infected with virus some time in his life. If children aged three years showed antibody, then we could be certain that the virus had been active in the last three years. When all mice of a group died, the serum contained no antibody. This is what happened with serum from the east coast towns of tropical Africa, from India or from Indonesia. Sometimes it might be found in an African community that a high proportion of persons aged over twenty years had antibody, but none under that age. This would point to an outbreak not necessarily at the clinical level twenty years previously without subsequent recurrence.

This is the sort of work that allowed the mapping of the areas in tropical Africa and South America where the jungle reservoirs of yellow fever lay, and where immunization of the population would be required.

The same mouse techniques developed in other directions led eventually to the production of an effective vaccine against yellow fever. But before that was possible another type of experimental animal had to be exploited. This time it was the developing chick embryo.

Growth of Viruses in the Chick Embryo and Other Embryonic Tissues.

The idea of using the chick embryo as a source of cells on which viruses could grow is due primarily to Goodpasture, but it can probably be claimed that work at the Hall Institute since 1934 has been to a considerable extent responsible for its development as a general method of virus investigation, particularly in relation to influenza viruses.[1]

As I have indicated, the chick embryo is of special significance in influenza virus research; but it is a most versatile tool, as may be indicated by the following list of the more important human diseases for which it has been used: small-pox and yellow fever, all forms of typhus and other rickettsial diseases, the many types of mosquito-borne encephalitis, influenza and mumps, *herpes simplex*, psittacosis, *lymphogranuloma inguinale*, rabies. All virus and rickettsial vaccines are now made by chick embryo methods with the exception of the prototype of them all, Jenner's vaccine against small-pox, and I have no doubt whatever in my own mind that if vaccination had been

[1] At this point a film prepared by Sir Macfarlane Burnet at the University of Wisconsin in 1952 was shown. It demonstrated the techniques used in the study of virus multiplication in the chick embryo, especially as applied to investigation on influenza virus.

discovered 150 years later than it was—in 1948 instead of 1798—the vaccine would have been grown in chick embryos and not in calves.

The chick embryo and the mouse have remained the sheet anchor of virus techniques but quite recently two new "experimental animals" have arisen. The first is the suckling mouse. If mice are inoculated in the first week of life, they are susceptible to a number of viruses which have no action on the older animals. This finding of Dalldorf's quite suddenly revealed that at least 16 different species of viruses passed irregularly through human communities as intestinal parasites. These are the Coxsackie viruses—so called from the little town in up-State New York where the first examples were found. They are responsible for some minor human ills, the most clearly defined of which are Bornholm disease and herpangina.

The suckling mouse has value for work on a number of previously known viruses, especially perhaps for foot and mouth disease of cattle and for the encephalitis viruses.

Finally we have the most recent success of them all, the application of tissue culture methods to poliomyelitis. People have used tissue cultures for growing viruses at least since 1926; but only in 1950 did this become a significant method in Enders's laboratory in Boston. The reason is simply that in the earlier work, although the virus grew, there was no way of knowing that it had grown short of testing the culture by transfer to some animal that suffered obvious symptoms as a result. If tissue culture was to replace monkeys for poliomyelitis research, the virus had to produce some effect on the tissue culture as definite as the paralysis in the monkey. Enders found two methods of doing this, and one of them has now been adopted all over the world as the standard approach to poliomyelitis virus studies. When fibroblasts from monkey testis or kidney are grown on roller tubes with a suitable nutrient fluid, the cells migrate from the original piece of tissue to form a sort of radiating halo around it. If they are infected by poliomyelitis virus, these migrating cells are killed and break down, losing particularly the actively radiating appearance. This change is easily visible with a hand lens, and it is easy to elaborate things so that we can determine whether any given fluid contains poliomyelitis virus, and hence develop methods of titrating virus and antibody.

Within the next two years this tissue culture technique promises to be as productive for the control of poliomyelitis as the mouse intracerebral method proved for the control of yellow fever.

The Significance of Technique.

To conclude this first lecture on the foundations of virology, may I first recapitulate the significance of these technical methods? Virology developed like any other science, only as fast as technical methods would allow. To handle viruses in the laboratory we have first to make use of the only way in which we can recognize their existence, by their disease-provoking power, and to find progressively more convenient objects on which such pathogenic activity could be recognized. Once a satisfactory way of detecting whether or not a given fluid or tissue emulsion contained virus was available, simple dilution techniques would allow titration of the virus, and appropriate mixtures in graded concentrations of serum with a standard dose of virus could be applied to the titration of the corresponding antibody. Suitable application of those two types of test will in principle at least allow the complete understanding of any infectious disease.

Sometimes we are not able to develop the necessary technical methods. There are still some important human diseases for which no suitable experimental animal has been discovered. Some produce a doubtful reaction in monkeys or anthropoid apes, and it may be well for our sense of proportion to enumerate them: trachoma and inclusion blennorrhœa, *encephalitis lethargica*, *herpes zoster*, chicken-pox, rubella, *molluscum contagiosum*, infectious hepatitis and homologous serum jaundice, and a whole series of respiratory infections, including the common cold. You will see that there are at least two great prizes still to be won. To establish the ætiology of hepatitis, especially serum hepatitis, and to find ways of preventing it would be the most valuable contribution any microbiologist could make to present-day medicine. And there are still some who hopefully look forward to the day when the common cold will be no more.

Finally, I shall mention very briefly the techniques developed since virology began to be sure of itself, by which some viruses can be recognized by means which do not depend on their power to produce disease. If the fluid from a chick embryo infected with influenza virus is mixed with a suspension of red blood cells, the cells are agglutinated in easily visible fashion. This hæmagglutination reaction is due to the virus particles sticking to the cell surfaces and can be used as a measure of the amount of virus present. This discovery revolutionized work with influenza almost overnight in 1941. Our own work on influenza virus in the Hall Institute has been very largely centred around the combined use of the chick embryo and the hæmagglutinin test. A number of other viruses will also agglutinate red cells in one fashion or other, and in some instances at least this character can be used for their titration.

A second method depends on the use of complement fixation methods. Extracts of heavily infected tissues usually contain an antigen which will show complement fixation with a corresponding immune serum. The technique used is basically similar to the Wassermann test. The complement fixation test is very often used in diagnostic or experimental work, but its interpretation is not always straightforward. In most cases the antigen is not the virus itself, but a smaller product of the virus-cell interaction.

I have left to the last the third method of demonstrating a virus other than by its disease-producing power. Many people would consider that the use of the electron microscope to show the size and form of virus particles is the most direct and obvious way of studying viruses. In fact, you have to know a great deal about viruses before you can hope to make a preparation that can be successfully photographed in the instrument. The electron microscope has some very important applications, but they are very little concerned with viruses as agents of infectious disease.

It was about 1940 that the techniques for virus study first became established. By the end of the war the tools were all available, and it is probably right to say that the concept of virology as an independent science has arisen only since 1945. There are other aspects of that development that I have had to leave aside. The most important is the influence that work on bacteriophages—the viruses that attack bacteria—has had in forming the general concepts of virology. However, I am one of those who in the last year or two have come to believe that the viruses responsible for human and animal disease are not so close to the bacterial viruses as we once thought. In these lectures I shall keep close to the viruses that are responsible for human disease. Within that range one can see a number of common characteristics with which I shall be concerned in the second lecture. Viruses pathogenic for bacteria, for plants and for insects also have some features in common with animal pathogens, but on the whole a clearer picture is obtained if we confine ourselves to one major group at a time.

To summarize: Virology as a science has developed essentially by the progressive improvement of techniques for laboratory study of the agents of virus disease in man. Where the nature of the virus has not allowed this development, progress has lagged—the common cold is the notorious example. Whenever means have been found for the quantitative study of a virus by methods requiring only a reasonable expenditure of money and effort, then theoretical understanding and practical control of the corresponding disease become possible. The mouse allowed the conquest of yellow fever, the chick embryo made us understand the behaviour of influenza viruses as well as we understand the tubercle bacillus, and from the appropriate use of fragments of monkey testis in tissue culture

we shall in a year or two have means of protecting our children from poliomyelitis.

In the next lecture I shall speak of ideas and general principles and try to show how virology is part of the embracing science of general biology.

FUNGOUS INFECTIONS IN HOSPITAL PRACTICE.

By E. BEATRIX DURIE and SHIRLEY BROWN.
From the Institute of Medical Research, The Royal North Shore Hospital of Sydney.[1]

CONANT and his associates (1944) wrote that "fungous infections are of such common occurrence that we have found it necessary to consider mycotic disease in the differential diagnosis of practically every obscure infection". Since the discovery of the newer antibiotics it has become even more important to keep the possibility of fungous disease in mind. Some potentially pathogenic fungi are normal inhabitants of the body; *Candida albicans* is the most notable instance of this. According to David Smith (1952), it can be isolated from the sputum of approximately 20% of normal individuals, from the skin of 30%, from the intestinal tract of 33%, and from the vagina of 15%. Various species of aspergillus, penicillium, geotrichum and cryptococcus are also found occasionally. *Actinomyces bovis* is found as a normal inhabitant of the mouth (Sullivan *et alii*, 1940); fortunately it is susceptible to the action of penicillin and other antibiotics. After prolonged treatment with the "broad spectrum" antibiotics, or with the combination of penicillin and streptomycin, latent or trivial infections with *C. albicans* may develop into severe or even fatal illness.

During 1949 we received a collection of type cultures of pathogenic fungi and of common contaminants from the University of California. This provided a stimulus and a background for work in the field of medical mycology. The collection has been maintained and added to from time to time; cultures have been received from and exchanged with the School of Public Health and Tropical Medicine, Sydney, with the Department of Agriculture, University of Sydney, with the Queensland Institute of Medical Research, and with other sources.

Examination of Lesions of the Skin.

Since June 1, 1949, it has been our practice to make cultures as well as direct examinations of material in the diagnosis of fungous disease of the skin. Previous to this, cultures for fungi had been made occasionally, but not as a routine procedure.

[1] Since January, 1953, this work has been assisted by a grant for part-time technical assistance from the National Health and Medical Research Council.

Methods.

Material was collected with sterile instruments, after the affected area had been thoroughly cleansed with 70% alcohol. It was plated out on Sabouraud's agar, at first at room temperature; later, when a special incubator was made available, at 26° C. Where indicated, material was also cultivated on blood agar at 37° C. The Sabouraud's agar used was made from the following formula: 18 grammes of granulated agar, 10 grammes of peptone, 40 grammes of brown sugar, one litre of tap-water. It was dispensed in small square glass bottles measuring 4·5 centimetres by 4·8 centimetres by 2·5 centimetres. Yeast-like organisms were transplanted to corn-meal agar, and *C. albicans* was identified by the characteristic chlamydospores produced on corn-meal agar, and by fermentation tests. The corn-meal agar used was made from "Quaker" yellow corn-meal imported from the United States of America; a 4% suspension in distilled water was steamed for one and a quarter hours; agar (1·5%) was added, then the whole was steamed for one hour, filtered through cheesecloth, tubed and sterilized. For semi-permanent culture mounts Dupont's "Elvanol" (polyvinyl alcohol) was used. A stock 15% solution was made up for use as follows: polyvinyl alcohol (15%), 56 parts; phenol, 22 parts; lactic acid, 22 parts; cotton blue dye or acid fuchsin, 0·05%.

TABLE I.

Number of Cases.	Result of Direct Examination.	Cultural Findings.
134	Positive.	Positive.
32	Negative.	Positive.
34	Positive.	Negative.
333	Negative.	Negative.
Total 533		

From June 1, 1949, to May 31, 1953, 533 cultures were made from skin scrapings, hair, vesicles and nails. In 134 cases, direct examination revealed fungus which was subsequently identified by culture; in 34 cases in which direct examination revealed no fungal elements, a pathogenic fungus was grown, and in 34 cases in which direct examination revealed spores or mycelium or both, no pathogenic fungus was grown. This latter group included two infections with *Malassezia furfur*; this fungus is not culturable. These results are summarized in Table I. Many of the patients

TABLE II.

Types of Fungi.	Areas Affected.											
	Scalp.	Face.	Body.	Axilla.	Groin.	Arms.	Hands.	Legs.	Feet.	Nails.	Ear.	Total.
Epidermophyton floccosum	—	—	1	2	3	—	—	—	1	—	—	7
Microsporum lanosum (vel canis vel felis)	63	—	—	1	—	—	4	1	—	—	—	69
Microsporum audouini ..	6	—	1	—	—	—	—	—	—	—	—	7
Microsporum fulvum ..	3	—	1	—	—	—	—	—	—	—	—	4
Trichophyton crateriforme ..	8	—	—	—	—	—	—	—	4	—	—	12
Trichophyton mentagrophytes (gypseum)	—	—	—	—	—	—	1	—	19	—	—	20
Trichophyton purpureum ..	—	2	—	—	—	1	—	—	2	3	—	8
Trichophyton rubrum ..	—	—	1	—	—	1	—	—	1	—	—	3
Trichophyton sulphureum ..	2	—	—	—	—	1	1	—	1	—	—	5
Sporotrichum schenkii ..	—	—	—	—	—	1	—	—	—	—	—	1
Hormodendrum pedrosoi ..	—	—	—	—	—	1	—	—	—	—	—	1
Nocardia asteroides ..	—	—	—	—	—	—	—	—	1	—	—	1
Candida albicans	—	—	4	—	6	—	2	2	7	5	—	26
Candida parakrusei ..	—	—	—	—	—	—	—	—	—	—	1	1
Candida tropicalis ..	—	—	—	—	—	—	—	—	—	1	—	1
Total	..	..	..	..	..	..	..	..	..	..	..	166

in whom no fungus was found had been sent to the laboratory to exclude fungous disease rather than to confirm the diagnosis of it. In a survey of fungous diseases in the Boston area, Downing *et alii* (1950) recorded positive findings by direct examination and culture in 186 of 829 patients presenting mycosis-like infections of the skin.

The types of fungi grown and the areas affected are shown in Table II. In many cases various areas of the body were affected; the lesions tabulated are those of which the patient chiefly complained. It will be seen that *Microsporum lanosum* appears to be the commonest cause of ringworm of the scalp in Sydney. This has been pointed out by Sharp (1951) and by other observers. All but one of the patients with scalp lesions due to *Microsporum lanosum* were children; the remaining patient was a woman, aged fifty years, with very soft dry hair, which had been permanently waved. In almost every instance there was a history of the child's having played with cats recently. The six infections of the glabrous skin with *Microsporum lanosum* occurred in nurses, some of whom were on duty in the children's ward. The culture of *Sporotrichum schenkii* was sent to us from another hospital; the culture of *Hormodendrum pedrosoi* was sent to us for identification by Dr. Hill, of Napier, New Zealand.

TABLE III.

Name of Fungus.	Number of Times Encountered as a Contaminant.
Acremonium	1
Acrostalagmus	1
Alternaria	7
Aspergillus glaucus	1
Aspergillus niger	5
Aspergillus sulphureus	1
Chætomium	3
Cunninghamella	1
Dematium pullularis	5
Fusarium	2
Gliocladium	2
Helminthosporium	6
Hormodendrum contaminant	7
Mucor	9
Nigrospora	1
Oospora	1
Pæciliomyces	2
Penicillium	30
Rhizopus	1
Rhodotorula	12
Saccharomyces	6
Scopulariopsis	4
Stenomyces	1
Streptomyces griseus	4
Trichoderma	4
Trichosporon	1
Trichothecium roseum	2
Ustilago	1
Verticillium	3

From 69 of the 533 cultures non-pathogenic fungi were grown, sometimes in mixed culture; these were identified when possible. Table III shows a list of these, with the number of times they occurred. Presumably these were skin contaminants, since the material for examination was collected with sterile instruments. It is important to identify these contaminants, if possible, as some of them may be confused with pathogens. It is our practice to clean the area to be examined with 70% alcohol; the more thorough this cleansing, the less is the likelihood of growing surface contaminants.

Lesions Other than Those of the Skin.

With regard to the culture of fungi from sources other than the skin, 442 miscellaneous specimens were cultivated for fungi during the period under review and the following results were obtained. *Histoplasma capsulatum* (Dowe *et alii*, 1953) was grown once, from an ulcer of the tongue; *Torula histolytica* (*Cryptococcus neoformans*) was grown once from sputum and once from cerebro-spinal fluid; *Geotrichum* was grown once from sputum and once from fæces; and *C. albicans* was grown 171 times from various specimens. Species of *Candida* other than *albicans* were encountered 29 times; of these, six were identified as *C. stellatoidea*, 10 as *C. krusei*, four as *C. parakrusei*, and two as *C. tropicalis*; seven strains were not classified. *Aspergillus sulphureus* was grown from pus from an empyema cavity and from sputum from the same patient; this fungus may, of course, occur as a contaminant, but in this instance examination of sections of lung removed at operation had shown a fungus resembling aspergillus in the wall of the lung abscess.

When tissue for biopsy is removed from a chronic granuloma, a portion should be placed in a sterile container, without fixative, for bacteriological and mycological examination. This will not always yield results, for organisms in such lesions, even when present, may not be viable; but it should always be tried. It is very disappointing, when histological examination of sections reveals bacteria or fungal elements, to realize that the opportunity for growing and identifying them has been missed. L. A. Weed and D. C. Dahlin (1949), of the Mayo Clinic, believe that "because of the inherent limitations of histologic procedure" every specimen removed for biopsy should be examined by cultural methods in an attempt to establish the causal agent. In many of their cases unsuspected fungous disease, or unsuspected bacterial infection, was revealed by culture.

Summary.

A short account of the incidence of fungous infections at the Royal North Shore Hospital from June 1, 1949, to May 31, 1953, is given.

Acknowledgements.

It is a pleasure to thank those members of the honorary medical staff of the Royal North Shore Hospital whose cases are referred to in this paper, and also Miss Shirley Rumble, whose technical assistance has been invaluable.

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THE SOUTH-WEST WIND.[1]

By CLIVE SANDS, M.B., B.S.,
Sydney.

WITH A NOTE ON THE METEOROLOGICAL ASPECTS BY

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ON September 19, 1952, I was troubled with paroxysmal sneezing, a runny nose, an irritable palate, irritable red and watery eyes, gastric disturbance, frequency of micturition, and a feeling of malaise—all symptoms of an allergic condition generally known as allergic rhinitis. From my observations at allergy clinics that I attend, in my own practice, amongst my friends and acquaintances, in public conveyances *et cetera*, I estimate that 100,000 people in Sydney were similarly troubled on that day and for the three days following. And that is a conservative estimate.

[1] Read at the annual meeting of the Australian Society of Allergists (British Medical Association) on July 23, 1953, at Sydney.

There was nothing unusual in this; it was merely the first of the spring south-westerly changes, a regularly occurring phenomenon at this time of year; it occurs at other times of the year also.

I have observed that this general response to a change of weather occurs especially with the south-west change, as far as Sydney is concerned. The "southerly buster" produces a response in a number of people, but it is not a general one, and it is apparently due to the change in temperature rather than to anything the air may contain. The trajectory is mainly over the sea. The direct westerly is a dusty wind at any time of the year; it is therefore troublesome to many, yet again it does not produce the general response of the south-westerly. The summer nor'-easter can be troublesome, but here again I consider that it is the cooling effect that is of importance. The trajectory is over the sea.

I decided to investigate the south-westerly further, and as a beginning I visited the Weather Bureau. Mr. A. K. Hannay kindly went into the question for me, and his dissection of the conditions is included in this paper.

It appears that the south-westerly often enters the continent at the head of the Great Australian Bight; it blows with a more or less westerly track, passing over Cootamundra and across the mountains, and arrives at Sydney with a south-westerly direction—that is, it passes over New South Wales south of the line drawn through Sydney–Cowra.

The westerly passes over the relatively poor country between South Australia and the Blue Mountains, north of the Murrumbidgee; the south-westerly passes over the Riverina and the relatively rich country south of the Murrumbidgee.

If we trace the trajectory in reverse, there is first the undulating country between the mountains and the sea, with its quantities of grass. Here we meet the common cause of allergic rhinitis, such as rye grass, plantain, couch grass *et cetera*. Apparently there are no surprises here for the allergist; but he knows that hyposensitization for these common reactors will not help a certain number of sufferers.

The next step brings us to the mountain country. Mr. L. D. Pryor, Superintendent of Parks and Gardens in Canberra, has suggested a more intensive research into the reactions of snow grass (*Poa cæspitosa*) and *Cassinia aculeata*. I still have an open mind on these as a possibility.

The next step brings us to the south-west slopes, characterized by the growing of wheat and by pastures. The latter produce enormous quantities of rye grass and many other grasses with whose reactions we are familiar. Probably there are no surprises here.

As we pass further west we come to immense areas given over mainly to natural herbage, and it is in these native plants that we must look for the reactors that appear to be almost universal in their devastating effect upon such a large part of the population.

I suggest that a native pollen is the unknown factor for many, because it is a wind of long trajectory over abundant vegetation that causes such widespread trouble.

To get some idea as to what might constitute the main wind-borne pollens of the districts, I visited the agronomists of the Department of Agriculture, and there Mr. K. R. Green made suggestions that are contained in a letter reproduced here.

> Further to our discussions on Friday last, the following plants might be considered as possible sources of pollen during September and October, and hence might be considered as possible hay fever plants.
>
> | | |
> |---|---|
> | *Helipterum corymbiflorum*
Helipterum strictum
Helipterum floribundum | Paper daisies |
> | *Calocephalus sonderi* | Buttons |
> | *Helichrysum* spp. | Everlastings |
> | *Craspedia richea* | |
> | *Erodium cygnorum*
Erodium moschatum | Crowfoot |
>
> The first six often occur over vast areas of Western Plain country, most particularly in the South West, although tending also towards the central western region.
>
> The Crowfoots are found very extensively in slightly better rainfall areas, but are probably not such prolific pollen producers.
>
> Another plant which might be worth considering is Slender Thistle (*Carduus pycnocephalus*) which is very widespread on the Southern Tablelands and South West Slopes, but is also found in most other parts of Eastern N.S.W.

In order to narrow the field, I wrote to our colleagues in Melbourne and Adelaide and asked for details of their most devastating allergic winds.

In the case of Adelaide, Dr. C. T. Piper tells us that the weather is dominated by the anticyclones moving across the Bight and the southern part of the continent in a west to east direction. These are modified to produce north-east to north-west winds as the main allergic menaces. This does not greatly help the present investigation.

In the case of Melbourne, Dr. Alan Murray gave me the following information:

> We think in Melbourne that the North Wind of Spring, especially November, is the worst wind as regards hay fever and associated Asthma.
>
> So far as the "Winds of Melbourne" are concerned, some Asthmatics say that any north wind affects them, Winter (July) or Spring; the Westerlies of September do not seem troublesome; Easterlies in February seem to accentuate some Asthma cases, and Southerlies in the main are welcome, as with few exceptions, they bring a cool change and relief from Easterly or Northerly weather.

The south-west line from Sydney intersects the north line from Melbourne about Deniliquin. That suggests that the western Riverina may be our suspect area.

Dr. N. C. W. Beadle, of the University of Sydney Botany School, has listed a number of plants for me that are to a certain extent confined to this area. Some of these in their habits are possible causes of trouble; others do not suggest a suitable form of growth. The problem is a very open one. The only method of solving it is a daily pollen count conducted over at least three years. Dr. Beadle's partial list of western plants is as follows: *Amphibromus neesii, Aristida behriana, Stipa densiflora, Xerotes leucocephala, Polygonum prostratum, Trichinium Spathulatum, Reseda luteola, Bergeria opara, Melaleuca pubescens, Heliotropium superum, Ajuga australis, Myoporum debile, Goodenia, Calocephalus sonderi, Eclipta platyglossa, Helichrysum semipapposum, Carduus pycnocephalus.*

A summary of Mr. Hannay's findings follows. I trust that he may be prevailed upon to study our problem in detail, and to explain to us why a certain wind can pick up and deposit pollen at distances often of many hundreds of miles from the source of supply.

Since September, 1952, we have had several periods of acute allergic activity—for example, on March 25, 1953. When Mr. Hannay investigated these it was found that the wind involved had a southerly origin, in the area between Tasmania and Macquarie Island, and that it had mainly a sea trajectory. This autumnal type of weather occurred in February and produced similar results.

This summer, 1953, the allergy season began early—in the second week in January; it generally does not commence till the fourth week in January, continues through February, and ends during the first week in March.

There was a succession of small "southerly busters" that created allergic trouble, and then on Tuesday, February 10, there was a change that caused widespread trouble.

An extract from a letter from Mr. Hannay reads as follows:

> An attempt to track back the air after its arrival in Sydney shows that (i) initially it had a rapid and short trajectory in N.S.W. coastal waters northward from Bega (i.e. in the evening of Monday 9th). (ii) But after about 3 a.m. on the 10th the air had a more recent land trajectory from the S.S.W.

The air was brought in by rapidly moving cold fronts, and was a cold outbreak rare in February, with low temperature, and very low humidity. The upper winds remained South or West of South at all levels after the arrival of the cold outbreak.

These autumnal changes serve to emphasize what I have previously recognized—that the factors involved in the spring and autumn are entirely different. Is the autumn factor an unrecognized tree-pollen or a fungus, or is it merely that secondary infections are more prone to develop in the autumn?

I feel that we shall have to ask Mr. Hannay to explain to us how pollen blown into the upper strata of air is again brought to earth.

I should like to emphasize again that a daily pollen count is the only method of satisfactorily answering this question, and it will require to include exploration of the upper atmosphere by slides exposed from aeroplanes, either commercial planes on regular routes or routine flights of the Royal Australian Air Force.

The South-West Wind: Meteorological Aspects.

(A.K.H.)

I have examined the origin and path of the air stream in the lower atmosphere upon certain dates in the spring, summer and autumn of 1952-1953, coinciding with periods of allergic activity.

The meteorological particulars concerning these dates and the day or so immediately preceding them were supplied to Dr. Sands in some detail, including (i) the point where the air stream entered the continent, (ii) its trajectory, (iii) its degree of turbulence, (iv) its speed in the surface and upper levels, (v) the depth and character of the air mass.

For the present purpose a summary should suffice (see Table I).

TABLE I.

Date of Arrival of Change at Sydney.	Track of the Air Mass.
September 19, 1952 ..	Adelaide-Cootamundra-Sydney about 7000 to 8000 feet deep.
November 2, 1952 ..	Head of the Australian Bight, then directly as a westerly; 5000 to 7000 feet.
November 4, 1952 ..	Originally from south-western Victoria, stagnated over eastern New South Wales, then brought quickly into Sydney by the formation of a wave (that is, a new local "low") on the associated cold front; quite deep.
January 6, 1953 January 9, 1953 January 15, 1953	All the week, cold-frontal passages of southerly or south-easterly type having sea trajectories, and not deeper than 5000 to 6000 feet initially.
February 9, 1953 ..	A cold and dry outbreak from the southern ocean via southern Victoria and the south-eastern tip of New South Wales; quite deep.
March 25-26, 1953 ..	A cold and dry outbreak from the neighbourhood of Macquarie Island.
April 4, 1953	From southern South Australia to Western Tasmania to Bass Strait to Gippsland, thence via Southern Tablelands. Not a "recent" cold outbreak, but a cooler and drier change.
May 20, 1953	From north-eastern Tasmania across Bass Strait and Gippsland. Before May 19 the air had come from the Bight, crossed the south-eastern part of Australia, and travelled right round a southern depression, which was a very slow-moving one.

The "plotting back" of the wind stream to find its origin and path is done by taking a series of synoptic weather charts for three-hour and six-hour intervals preceding each other. One uses the "gradient wind" as expressed by the isobaric pattern to represent the direction and speed of the air flow. The technique then is to "track back" from chart to chart. There are limitations to this method, these being mostly due to vertical motion and the effects of condensation in the air stream; but in spite of this it is reasonably reliable, especially with a fairly strong wind field. For high levels trajectories can be worked out in a similar way from upper contour maps.

South-west changes at Sydney are features of autumn, winter and spring. In the ten cases mentioned above, all were changes between west and south-south-west except those in January. The February change was a rare type for that month, since those of February are usually the southerly "burster" type.

The three spring changes definitely brought in air which had crossed the lower western or Riverina areas. The summer and autumn cases involved air from other regions, as shown.

The south-west air stream behind a cold front is normally turbulent and often has a temperature inversion associated with it. The pollen would move freely with the stream and the inversion would hold it down below a certain height.

There is a pronounced fall of temperature after the southerly "burster" (sea trajectory) type of cold front. In the south-westerly type there is only a small fall of temperature and, when the air arrives as a westerly, hardly any. These remarks do not apply to the winter season. Humidity is always less with the latter type of change.

In addition to vertical motion and turbulence in the air, there are compensating subsidence processes. High-pressure systems, which move across the continent (except in summer, when they drift erratically over southern ocean areas) after being "ushered in" by cold fronts, are noted for downward movements of the atmosphere.

More often than not the wind drift at high levels (say 10,000 feet upwards) has a westerly component. During periods of east coast cyclonic weather the high level drift is "easterly". There would never be a state of stagnation for more than a day or two at most, and so there could not be a more or less stationary "reservoir" of pollen.

There is a literature on the subject of diffusion in the atmosphere (chiefly in connexion with industrial smoke pollution) and also on atmospheric turbulence.

Some information on the atmospheric transport of silver iodide and zinc sulphide particles can be given, with acknowledgement to the Commonwealth Scientific and Industrial Research Organization. Although these are smaller than pollen with diameters of 1·0μ and 2·0μ respectively, their behaviour with a west or south-west stream may be comparable, since the pollens (about 20μ) would possibly be as buoyant on account of their structure.

The Commonwealth Scientific and Industrial Research Organization experiments have been conducted from the Riverina and from Dubbo in the central west in the neighbourhood of cold fronts with west or south-west air streams. The material was ejected as a "smoke" from generators on the ground.

Table II shows the relation between the plume width (that is, the width of the stream of "smoke") and the horizontal distance from the point of ejection, for zinc sulphide.

TABLE II.

Distance Downwind. (Miles.)	Plume Width. (Miles.)
10	6
20	10
40	17
100	25

After 100 miles the depth of the layer was two miles (about 10,000 feet). At this distance the concentration of the particles was found to be anything but regular, and no particular preference was shown for the high levels. The maximum distance for which examination has been made so far is 135 miles, at which stage a steady state (that is, a more or less constant plume width) had not yet been reached.

The examination was carried out from an aeroplane, the zinc sulphide being detected by the fact that it is fluorescent. A further report on the behaviour of zinc sulphide will soon be forthcoming, with information on its penetration to greater distances down wind.

Dust, picked up by turbulent winds in inland Australia, has been deposited in New Zealand and in the Tasman Sea. As was stated by Loewe, in Bulletin Number 28 of the Commonwealth Meteorological Bureau, the most frequent size of dust particles in dust storms is 10μ. The average velocity of fall of dust particles is given as about one centimetre per second. The settling velocity for pollen (in still air) would be of the order of a few millimetres per second.

PROBLEMS IN FERTILITY AND STERILITY DUE TO ECTOPIC PREGNANCY: A STUDY OF 259 CASES.

By ALAN GRANT, F.R.C.S., M.R.C.O.G.,
Sydney.

IT is a common practice for the occurrence of an ectopic gestation to be regarded as an unlucky event that will in no way prejudice a woman's chances of becoming pregnant at a later date, and this information is conveyed to the patient.

A study of the real facts will reveal this piece of optimistic philosophy to be without any clinical foundation, and indeed less than one-third of the patients who have suffered from this reproductive disaster will ever produce a living child.

This paper has been divided into discrete parts in an attempt to answer several questions bearing on the relationship between ectopic pregnancies and sterility. The result of the relevant investigations will be set out under the title of the appropriate question.

The Material Studied.

The patients studied in this paper have been those found in two separate departments of the Women's Hospital, Crown Street, Sydney.

In the first group they were ordinary gynæcological out-patients. Out of a total of about 13,000 out-patients there were 100 consecutive women who had suffered from an ectopic pregnancy—an incidence of one case in 130 patients. We examined these with a view to discovering whether they had suffered from sterility since the operation for ectopic gestation.

In the second group there were 133 women who had attended a different department of the hospital—namely, the Sterility Clinic—because of their inability to become pregnant after an ectopic pregnancy.

There were 26 patients who developed an ectopic pregnancy during their treatment for sterility.

In all, therefore, there were available for investigation 259 women who had had operations for ectopic pregnancy.

Does the Occurrence of Ectopic Pregnancy Cause Subsequent Sterility?

In order to find an answer to the question whether ectopic pregnancy causes subsequent sterility, we examined the group of 100 ordinary gynæcological out-patients who had suffered from an ectopic pregnancy and who attended the gynæcological department for some complaint other than sterility.

Amongst these patients approximately 60% had their ectopic pregnancy in the right Fallopian tube. There were only a few patients who did not know what tube had been the site of the pregnancy. We were surprised to find that only 22 of these patients had been able to produce a living child since their operation. As only 10% of those questioned admitted the use of contraceptives, and as many of the preventive techniques were obviously faulty or inadequate, it therefore appears that about 68% had been unable to give birth to a living child. A total number of 43 patients had become pregnant after the ectopic gestation, but only 22 of them had given birth to a living infant, the remainder having had miscarriages or a further ectopic pregnancy.

The findings are borne out by a study of the world literature on the subject, as Bret (1947) found that only 30% of his patients were successful in producing a living infant, while Giovanni and Wirtz (1949) quote a figure as low as 15% in their cases. Siegler (1945) made an estimate that in his group of patients the figure was not over 20%.

It is therefore established that the occurrence of an ectopic pregnancy does tend to cause subsequent infertility, and that not more than one-third of these patients who have suffered from an ectopic pregnancy can hope to produce a live infant.

What Are the Causes of Sterility in the Patients Who Have Had an Ectopic Pregnancy?

We were in a favourable position to determine the causes of sterility following an ectopic pregnancy, as we found that there had been 133 patients in the Sterility Clinic of the Women's Hospital, Crown Street, who had suffered from sterility for a year or longer after the occurrence of an ectopic pregnancy. One of these had had an ovarian pregnancy (1953) and the rest had had tubal gestations.

All these women and also all their husbands had been well studied in the clinic, and the causes found to account for the women's inability to become pregnant are set out in Table I, the tubal factors being in the first grouping.

TABLE I.

Sterility Factor.	Number of Patients.	
Residual blocked Fallopian tube	58	88 (67%)
Patent hydrosalpinx	6	
Peritubal adhesions	13	
Tubal stenosis without peristalsis	11	
Recurrent tubal spasm	2	
"Doubtful" tubes (patient pregnant after one Rubin's test)	17	
Male sterility (no sperms)	7	
Anovulation	3	
Underdeveloped premenstrual endometrium	2	
Cervical barrier with patent residual tube	11	
Secret contraception	2	
Endometriosis	1	
Total	133	

It will be seen that 67% of patients had sterility that was definitely of tubal origin, whilst 81% had presumably a tubal cause for their failure to conceive, because 17 patients who had been sterile for one year or more promptly became pregnant after the performance of one Rubin's test.

Therefore 107 patients (or 81%) were probably victims of sterility due to tubal causes, and 67% of cases of sterility were incontrovertibly of tubal ætiology.

Rubin (1947) found that 85% of women who had had a previous ectopic pregnancy were suffering from blocked or damaged Fallopian tubes.

It is therefore reasonable to conclude that the sterility factors operating in women who are not able to conceive after an ectopic pregnancy are predominantly tubal in origin, though not exclusively so, as a study of the second half of Table I will indicate.

Is Ectopic Pregnancy Common Amongst Patients Treated for Sterility?

During the last seven years, 3725 new patients have been examined at the Sterility Clinic of the Women's Hospital, and an analysis of the results of the pregnancies that occurred in this group was made. There were 1214, or 33% of all patients suffering from primary or secondary sterility, who became pregnant. This figure we refer to as the "absolute pregnancy rate", and it has been described in a previous paper (Grant, 1951), and includes all the patients examined whether the cause of their infertility

was obviously irremediable or not. The results found in this group of pregnancies are set out in Table II.

It will be seen that there were at least 26 patients with ectopic pregnancies, all pregnancies except one being located in the Fallopian tube. This gives an incidence of about 2·0% for the occurrence of ectopic pregnancy in our series. This figure is seven times greater than has been found by Schuman (1924) to be the usual one. His findings indicated that one pregnancy in every 303 was ectopic in origin, whereas our patients were affected once in every 50 pregnancies.

TABLE II.

Analysis of 1214 Pregnancies Occurring in 3725 Cases Investigated at the Sterility Clinic in Seven Years.

Outcome of Pregnancies.	Number of Cases.	Total.
Miscarriages:		
At the Women's Hospital	108	132
Elsewhere	24	
Ectopic pregnancies:		
At the Women's Hospital	23	26
Elsewhere	3	
Living infant delivered:		
At the Women's Hospital	677	769
Elsewhere	92	
Patient not confined:		
At the Women's Hospital	61	83
Elsewhere	22	
No record of confinement	204	204
Total	—	1214[1]

[1] That is, 33% of 3725 cases investigated.

This figure at first sight appears to be a startling one; but one must allow for the fact that in our clinic we treat a large number of patients who are sterile because of blocked or damaged Fallopian tubes. The women are treated for the most part by the high-pressure insufflation of carbon dioxide at 300 millimetres of mercury and ultimately by an injection of iodized oil or of an aqueous medium at the same pressure. At many clinics such patients are recommended to adopt an infant, and no attempt is made to rectify the condition of blocked Fallopian tubes.

A survey of the literature on the subject of how frequently an ectopic pregnancy occurs amongst women treated for sterility indicates that all authors and investigators have an increased incidence to report.

Bender (1953) recorded 1·7% ectopic pregnancies occurring in a group of 42 pregnant patients.

Mazer and Israel (1951) also found a similar number of these misplaced gestations.

Kaplan (1950) gives the incidence as 1·3%.

Rubin (1947), working with a group of 590 patients, found an incidence of ectopic pregnancy reaching as high as 2·2%.

Ectopic Pregnancy After Treatment for Blocked Fallopian Tubes.

We have already indicated that it has been the custom at this hospital for the last six years to treat many patients with tubal blockage by the insufflation of carbon dioxide at pressures greatly in excess of those advocated in text-books on the subject (Grant and Mackey, 1948).

In a group of 370 patients treated for blocked Fallopian tubes by pressure insufflation over the last six years, the frequency of ectopic pregnancy was 25 times that found in the normal pregnant members of the community. This series of patients who had presented themselves with blocked tubes produced 65 living infants. It will always be a matter of opinion whether the treatment was worth the expended effort. It was our aim at the time to make a clinical investigation into whether it was possible to blow tubes open at a pressure in excess of 200 millimetres of mercury, and in addition to discover whether such a high pressure of carbon dioxide was safe. The conclusion we have arrived at is that there is no danger involved, and therefore the old dictum that a pressure in excess of 200 millimetres of mercury is dangerous should be revised—always provided that the gas used is none other than carbon dioxide.

Ectopic Pregnancy after Plastic Operations on the Fallopian Tubes.

We have had only one ectopic gestation after plastic operations on the tubes in a group of 65 patients. This is probably because we have had no more pregnancies in this group than Greenhill (1939) promised in his much-quoted survey of the results of tubal plastic operations.

We have been increasingly successful in obtaining patency of the tubes after these surgical plastic procedures, but there has not been an equal progress in the number of ultimate pregnancies.

Repeated Ectopic Pregnancy.

The recurrence rate of tubal pregnancy in our clinic has been about 5%. The usual expectation of a second ectopic gestation has been estimated in the literature at a figure between 3% (Siegler, 1945) and 10% (Haffner, 1940).

We have observed one patient who suffered from three such tubal pregnancies. One tube was removed for the first ectopic pregnancy, and at the operation for the second one a tubal mole was removed to conserve the appendage. However, a third ectopic pregnancy occurred in the conserved tube and it was ultimately removed.

Caffier (1942) reported 10 cases in which he conserved the tube; but only three patients produced live babies subsequently.

TABLE III.

X-Ray Examination.	Number of Cases.
No X-ray examination performed prior to ectopic pregnancy	5
X-ray examinations performed, showing both Fallopian tubes patent	13
X-ray examinations performed, showing one tube patent	5
X-ray examinations performed, showing blocked or damaged tubes on both sides	3
Total	26

Was the Residual Fallopian Tube Damaged Before or After the Ectopic Pregnancy?

When a complete investigation is carried out on patients who have already been operated on for ectopic pregnancy, we have shown that at least two-thirds of them will be found to possess a residual tube that is damaged or blocked.

The question arises as to when this tube suffered its pathological change. Was it during an attack of salpingitis before the occurrence of the ectopic gestation? Or on the other hand, was it during the post-operative convalescence from the operation of salpingectomy?

In our series of patients who had developed an ectopic pregnancy whilst under treatment for sterility there were available for study 21 salpingograms that had been taken prior to the pregnancy, and an examination of these X-ray plates indicated that both Fallopian tubes had originally been patent in 13 cases. Therefore, more than half of these women had their residual tube damaged during the convalescence that followed the operation of salpingectomy. The results may be better followed from a study of Table III.

The three patients recorded as having both tubes blocked or damaged prior to the occurrence of an ectopic pregnancy were able to become pregnant as a result of therapy directed against these conditions.

Most of the patients who attend the Sterility Clinic are subjected to both a Rubin's test and salpingography soon after their first attendance. We carry out this double investigation because we consider the function of the clinic to be one of research as well as that of a unit for diagnosis and treatment.

Discussion.

It appears to be established, both by the statistics in our own hospital and from a survey of the world figures, that the occurrence of an ectopic pregnancy is a major accident for the patient who wishes to produce a family, because, at the best estimate, only one-third of such patients will ever succeed in having a live baby, and in many groups the obstetric prognosis is much worse. Some investigators found that only one in every six of them had a live baby during the rest of their life.

When we come to inquire into the causes of this sterility, we find that it is located in the Fallopian tubes incontrovertibly in 67% of our cases, and that most likely the tubal factor operating is in the vicinity of 81%.

In Table I we have presented an analysis of all the causes of this inability to produce a living child, in a series of 133 patients.

The suspicion that sterility patients are more likely to have an ectopic pregnancy than their normal married sisters is confirmed and amplified by a dissection of the cases found in the Sterility Clinic attached to this hospital. Sterility patients are about seven times more likely to be victims of a misplaced pregnancy. Bender's statement is correct in which he suggests that "presumably tubal dysfunction is the chief factor in the increased ectopic rate" (Bender, 1953).

Thus we find that an ectopic pregnancy causes subsequent sterility in at least two-thirds of the patients, and conversely that sterility patients are seven times more likely to have such a misplaced pregnancy than other women. Into the sad story of sterility is woven the black thread of tubal pregnancy.

Our evidence concurs with that found by Rubin and suspected by many that this trouble is located in tubal damage.

The prevention of a tubal pregnancy revolves round the prophylaxis of tubal damage by the prevention of self-induced abortions and by the early treatment of other infections, and in addition by making sure that every patient operated on for an ectopic gestation is left with a normally patent residual Fallopian tube.

In the case of those patients who fail to become pregnant after having been operated on for an ectopic gestation, there may be some doubt whether the damaged residual tube that most of them possess was so affected before or after the surgical operation that was performed.

An examination of our cases, as set out in Table III, indicates that the one remaining tube was damaged after the operation in about 50% of the patients. One must conclude that there is some fault in the usual operative technique for the treatment of ectopic pregnancy or in the subsequent post-operative régime.

Some of this tubal impairment may be due to the late diagnosis of the so-called "leaking ectopic". In these cases puncture of the posterior fornix with a needle or the use of the culdoscope may aid an earlier diagnosis, and can do little harm if antibiotics are administered forthwith.

The text of this paper is to suggest that no patient has been properly treated for her ectopic pregnancy until her one remaining Fallopian tube has been protected by antibiotics after operation and subsequently proved patent to carbon dioxide by the performance of a tubal insufflation as a routine procedure. Salpingography can be used as a substitute, but in this case the use of an aqueous medium is desirable.

In the reproductive life-history of any woman an ectopic pregnancy is always an unwelcome accident; but these investigations indicate that, in addition, it is often an irremediable and major disaster.

Summary.

1. After the occurrence of an ectopic pregnancy, less than one-third of the patients will succeed in producing a live baby for the rest of their reproductive life.

2. The causes of this subsequent sterility are mainly tubal in origin, and are detailed in Table I.

3. The incidence of ectopic gestation in patients attending a sterility clinic is seven times the usual incidence, when they become pregnant.

4. The frequency of ectopic gestation in patients treated for tubal blockage by high-pressure insufflation is 25 times that found amongst the rest of the pregnant members of the population. The alternatives are to do nothing or to operate. However, tubal plastic operations are not yet very successful in the hands of any surgeon. It is not difficult to succeed in rendering the Fallopian tube patent, but very few of the patients bear a live baby subsequently.

5. The damage to the residual tube in most of the patients who have had an ectopic pregnancy appears to have been inflicted on them after the salpingectomy in 50% of cases. The other 50% suffered bilateral tubal damage at the time of the original septic lesion in the pelvis, which preceded the occurrence of the ectopic gestation.

6. No patient has been adequately treated for an ectopic pregnancy until her one residual tube has been proved patent by subsequent insufflation with carbon dioxide or by salpingography with the use of an aqueous and non-irritating medium.

Acknowledgements.

The work in the Sterility Clinic is done by a cooperative team. I should like to thank especially Dr. Robert Mackey and Sister M. Johnson for their assistance in the management of the patients, and also Dr. Bruce Lee, Dr. Phillip McBride, Dr. R. Lewis and Dr. Colin Love. Dr. Murray Moyes has been in charge of the pathological work, and I wish to thank him for the special interest he has shown in the activities of the Clinic.

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PENICILLIN SENSITIVITY.[1]

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BEFORE penicillin sensitivity is discussed let us briefly review its manufacture. From the first therapeutic trials of penicillin by Sir Howard Florey and his colleagues, up to the present, all the penicillin used clinically has been produced by biological synthesis by various strains of the mould *Penicillium*. Penicillin has been synthesized in the laboratory; but all the indications are that for clinical use production costs of artificial synthesis will prohibit replacement of the currently used biologically produced drug.

Early in the history of penicillin production the mould was grown on the surface of still liquid media. Towards the end of World War II the bulk of production was from submerged, aerated, agitated culture in 5000 to 10,000 gallon fermentation tanks, and this method is now, for practical purposes, the source of all penicillin available to the medical profession.

The essential ingredients of the medium in which the mould is grown are corn-steep liquor, lactose, inorganic salts and penicillin precursors, such as phenyl-acetic acid. Anti-frothing agents, essentially higher aliphatic alcohols, are added during the growth period. Corn-steep liquor is the liquid obtained after the preliminary digestion of maize in the manufacture of starch. Its composition is somewhat variable, but it acts as the main source of nitrogen for growth of the mould, and in addition provides some carbohydrate and inorganic salts.

When penicillin production in the fermentation tank has reached its peak, the penicillin-containing broth is separated from the mould mycelium by a process of vacuum filtration. The broth is then subjected to a series of extractions with organic solvents—for example, amyl acetate—which result in concentration of the penicillin in a much smaller volume of solvent and a considerable degree of elimination of impurities. Final stages include filtration through bacterial filters to ensure sterility and to remove pyrogenic substances, and precipitation in the crystalline form of the sodium or potassium salts, or freeze-drying of final purified solutions of the calcium salt to produce the dry amorphous calcium salt.

By definition in terms of an international standard, the potency of pure sodium penicillin is 1667 units per milligramme. Current production methods have reached such a standard that much of the penicillin used clinically—and this applies especially to the crystalline sodium, potassium and procaine salts—practically attains this level of theoretical potency. In view (i) of the early demonstration that pure crystalline sodium penicillin proved antigenic in human subjects, (ii) of the tremendous improvement in the purity of penicillin used clinically in the last five or more years, and (iii) of the unlikelihood that the traces of impurities now present in commercially produced penicillin will be eliminated, it would seem that for practical purposes clinicians should accept allergic reactions developing after penicillin therapy as almost certainly the result of the penicillin molecules. It would appear that any attempt to distinguish in practice between reactions due to penicillin and those due to associated traces of impurities would present almost insurmountable difficulties.

In procaine penicillin preparations "tween 80", a sorbitan monoleate, is used as a wetting agent, and carboxymethyl cellulose is used as a suspending agent; these two substances are considered to be 100% inert biologically. Sodium citrate is present as a buffering agent in most readily prepared suspensions.

Oil has just about fallen into disuse, but beeswax, peanut oil and aluminium monostearate have been used. These have been shown to be the cause of subcutaneous nodules and sterile abscesses. Benzyl penicillin is used in this country.

[1] Read at a meeting of the Section for the Study of Allergic Diseases of the Victorian Branch of the British Medical Association on August 6, 1953.

Penicillin is concentrated by the kidneys and is present in the urine for about twenty-four hours after an intramuscular injection. It does not pass freely into the cerebrospinal fluid. Massive oral doses are necessary to achieve therapeutic blood levels.

Toxicity.

Although penicillin is generally non-toxic, there is no question but that nervous tissue is vulnerable to the action of the drug. Walker and Johnson (1945) have reported the development of convulsions in a patient following intraventricular administration of penicillin, and Sweet *et alii* (1945) described neurological complications after intrathecal administration of penicillin. Lozenges and sprays of penicillin may produce "black tongue" and stomatitis, probably due to the unrestricted growth of the fungus *Monilia albicans* made possible by the suppression of the normal oral flora by the antibiotic. Jarisch-Herxheimer reactions occur in syphilitics (Shaffer and Shenkin, 1950), and have followed the use of penicillin in both early and late cases. Deaths have been reported.

Penicillin has definite antigenic properties. Sensitization attributes have been demonstrated by positive results to intradermal tests, by indirect or passive transfer (Prausnitz-Kustner) and by precipitin tests (Urbach and Gottlieb, 1946).

The early belief that allergic reactions to penicillin were connected exclusively with the impurities has been thoroughly discredited by the mass of data to the contrary in the literature (Welch and Lewis, 1951).

Incidence.

Rostenberg and Welch (1945) showed that of 144 persons tested, 5% exhibited a positive reaction of the tuberculin type, despite the fact that none of these subjects had had previous contact with penicillin. Thomas *et alii* (1948) found that there were 2·5% reactions in 10,000 patients treated with penicillin, while Lepper *et alii* (1949), in a comparative study of different penicillin preparations used to treat 1303 patients, found that the incidence of reactions was as follows: aqueous benzyl penicillin, 1·2%; benzyl penicillin suspended in oil or beeswax, 2·7%; procaine benzyl penicillin suspension in oil, 1·4%. A high dosage of benzyl penicillin in aqeuous solution—namely, 500,000 units every two hours—increased the incidence to 7·8%. Sensitivity to penicillin seems to be uncommon in children.

Types of Reaction.

Immediate reactions usually occur in persons with a known history of penicillin sensitivity or at least with previous exposure to penicillin, although a small proportion seem to be spontaneously or naturally sensitive. It is questionable whether natural sensitivity really exists without previous exposure, as these persons may possess a sensitivity to fungi. Acquired sensitivity may be produced by repeated injections or by repeated local applications. It is important to stress the difference between common delayed reactions and uncommon immediate reactions, the latter including accelerated reactions.

Symptomatology.

Penicillin as a contactant may cause "contact dermatitis", or it may affect the eyes when drops of penicillin solution are used.

As an inhalant in aerosol therapy, penicillin may cause asthma.

Both as injectant and as an ingestant, penicillin may cause sensitivity symptoms.

A common reaction to penicillin is urticaria, which may be either of the ordinary or of the giant type. There may be intense itching. Another frequent manifestation is similar to serum sickness with fever, albuminuria and arthralgia, with or without urticaria. Asthma may occur in the more severe reactions. Other skin lesions have been described. Lamb (1945) described apparent cross-sensitization, when a skin site which had previously been infected with ringworm fungus showed erythemato-vesicular eruptions. Cohen (1951) described atopic dermatitis following penicillin

injections in a female patient, aged two years, while Rubens (1951) described a local hæmorrhagic-necrotic lesion occurring in the buttock of an infant.

Rabinovitch and Snithkoff (1948), Shaffer (1948) and Berne (1950) report maculo-papular lesions followed by exfoliative dermatitis. Purpura and nephritis after injection of procaine penicillin were reported by Spring (1951). Cardio-vascular allergy described by Harkavy (1952) occurred in four allergic subjects receiving both penicillin and sulphadiazine. Symptoms occurred one to two weeks after treatment for respiratory infection, and polyarteritis, pulmonary infiltration and purpura followed. Post-mortem examination revealed necrotic arterial lesions, widespread foci of myocardial scarring, granuloma of the aorta and necrotic lesions in the liver.

Acute anaphylactic shock and death usually occur soon after the injection is given. So far eight fatal cases have been reported (Waldbott, 1949; Wilensky, 1946; Thomson, 1952; Higgins and Rothchild, 1952; Siegal *et alii*, 1953; Mayer *et alii*, 1953), and two cases were reported by Curphey at a meeting of the Academy of American Sciences in March, 1952 (Siegal, 1953). It is significant that four of these patients were asthmatics, while the others had never had any type of allergic symptoms. Non-fatal anaphylactic reactions have been noted by several observers, including O'Donovan and Klorfajn (1946), Burleson (1950), Everett (1951), Siegal *et alii* (1953) and Mayer *et alii* (1953).

Factors in the Acquisition of Penicillin Sensitivity.

The size of the dose is probably a factor in the acquisition of penicillin sensitivity. Repeated injections and a long interval between the courses of treatment seem more likely to produce sensitivity. Physicians, dentists and nurses who handle penicillin seem to be particularly prone to develop sensitivity. When doctors and nurses are squirting air out of a syringe preparatory to giving a penicillin injection, a fine spray may be produced which may be inhaled and so gradually induce sensitivity.

Prophylaxis.

It is obvious that the indiscriminate use of penicillin should be avoided; in minor infections of the upper respiratory tract chemotherapy should be avoided altogether. Oral therapy seems to produce fewer untoward reactions. Before penicillin is given, ask about previous injections and whether they produced any local or general reaction. Immediate reactions are more important than delayed reactions; but absence of a previous history of allergy to the drug does not necessarily rule out the possibility of anaphylactic sensitization. Great care should be taken with a case of exfoliative dermatitis or contact dermatitis due to penicillin.

The possibility of an idiosyncrasy to procaine must be considered when procaine penicillin is used. Although procaine is probably the least toxic of the cocaine group, it sometimes causes systemic effects in hypersensitive individuals. Martindale's "Extra Pharmacopœia" (1952) reports deaths from as small a dose as ten milligrammes. The symptoms are nausea, vomiting and abdominal pain and rapid pulse, and the respiration becomes irregular, and these could be confused with an anaphylactic reaction to penicillin. Usually the content of procaine in, say, a 400,000 unit preparation of penicillin is 120 milligrammes. Shaw (1953) states that sensitivity to procaine can be induced by repeated injections, but about 30 to 40 injections are needed. I have tested about 400 subjects, including all my penicillin-sensitive patients, with an intradermal injection of 1% procaine solution, but have not had a positive reaction. This does not rule out the possibility of procaine sensitivity; but I have gained the impression that procaine was not the cause of reactions in any cases I have encountered, except possibly in one case which I shall mention later.

Skin Tests.

As impurities in penicillin preparations are unknown and not isolated, it is impossible to make tests with these. For testing I have used scratch and intradermal tests. For scratch tests a solution containing 50,000 units of penicillin per millilitre was used, and in each case four different brands of commercial penicillin, two being crystalline and two containing procaine penicillin, were tested. A control scratch test with buffered saline was made after each penicillin test. Intradermal tests were performed by injecting 0·03 millilitre of a solution containing 1000 units of sodium penicillin per millilitre and a control test with buffered saline. Immediate results were observed in fifteen minutes, and in the case of a delayed intradermal test twenty-four to forty-eight hours later. A result was regarded as positive when erythema, weal formation and itch occurred, provided that the control tests gave negative results, and in the case of a delayed result an area of erythema at least one inch in diameter. I have performed the above-mentioned tests on about 100 subjects with no history of penicillin sensitivity, and no positive reactions were obtained.

The number of cases I present for analysis is small, but may give some guide as to the value of skin tests. The patients are divided into two groups: (i) those who developed symptoms within forty-eight hours after an injection of penicillin, the immediate or accelerated type; (ii) those reacting after a longer interval, the commoner delayed type of reaction. There were 12 cases in which symptoms were immediate or accelerated and came on within forty-eight hours. Four of these patients had acute anaphylactic symptoms with asthma and severe giant urticaria. Four of the patients reacted to scratch tests, a positive reaction being given to each brand of penicillin tested; two of the patients with anaphylactic symptoms did not react. Of the remaining eight patients only one reacted to an intradermal test. Therefore seven patients did not react in this group at all.

There were 15 patients whose symptoms had come on after three days or more, the average time of onset being ten days. Seven had suffered from giant urticaria, five from erythema and intense pruritus, and three from an ordinary type of urticaria. A scratch test produced a positive reaction in two cases only, and in these two severe giant urticaria started fourteen days after the last injection. Of the remaining 13 cases, only five reacted to an intradermal test, so eight patients did not react in this group. Surveying these results, one is impressed with the unreliability of skin tests, as only 12 of 27 patients reacted to either scratch or intradermal tests. Of the 27 patients tested, three were asthmatics and had severe accelerated symptoms, while four suffered from hay fever but did not have accelerated symptoms. There were three physicians and six nurses among the subjects tested. The severity of symptoms was sometimes not related to the time of onset, as three who developed severe symptoms of swollen tongue and probable glottic swelling had had their last injection about twelve days previously.

The foregoing results with scratch and intradermal tests would suggest that a careful clinical history of previous untoward episodes after penicillin therapy is much more important than relying on skin tests to detect sensitization. It is important to note that in every case in which a positive response to a skin test was obtained, penicillin had been given prior to the injections that produced symptoms; this suggests the importance of induced sensitivity.

Patch tests appear to be unreliable; but two nurses with dermatitis of the hands showed a positive reaction to an ointment containing 1000 units of penicillin per gramme. Penicillin eruptions are mostly urticarial; this indicates a sensitization of the blood vessels in the dermis, and may explain why patch tests are unreliable and scratch and intradermal tests are more useful. According to Wartzki (1953), patients under treatment with cortisone can be tested without risk of a flare-up, but in others there is a risk of exacerbation of symptoms.

Five of the cases in which severe symptoms developed are worth considering in more detail.

A woman, aged forty-two years, had suffered from fairly severe asthma since childhood, and had a course of procaine penicillin for a breast abscess without any reaction. Eight

weeks later she had a further course of procaine penicillin for pneumonia, and two days after the last injection she developed severe asthma and giant urticaria, which persisted for five days. Scratch tests produced immediate large reactions.

A woman, aged twenty-three years, had been treated with crystalline penicillin five years previously for scarlet fever; two years later crystalline penicillin was given for an infected finger, and symptoms of giant urticaria resulted. Three years later an injection of penicillin was given after a tooth extraction, and immediately she developed a swollen tongue, her face became grossly œdematous and her breathing was difficult for several hours. Scratch tests produced large positive reactions. It would be extremely dangerous for her to have another injection of penicillin.

A man, aged sixty-four years, had had procaine for teeth extractions without ill effects, but no penicillin. He was given procaine penicillin for "influenza", and one hour later developed numbness in the legs and arms, vomiting, palpitations and shortness of breath, which lasted for several hours. All skin tests produced negative results, including one with procaine. This patient, as his physician thought, may have been sensitive to procaine.

A woman, aged fifty-four years, in 1946 had a course of injections of penicillin for syphilis. She had two more courses in 1951 for the same condition without any reaction. In 1953 she developed pneumonia and was given crystalline penicillin, 100,000 units every six hours for four days. After the second last injection she had symptoms of urticaria almost immediately, but these were disregarded. Ten minutes after the next injection of penicillin she developed œdema of the glottic area and intense generalized itching; the symptoms gradually subsided in two days. She had suffered from hay fever and asthma earlier in life. Skin tests with penicillin and procaine gave negative results.

A man, aged twenty-nine years, had penicillin injections in 1948 after a nasal operation; in 1951 he was given penicillin lozenges for tonsillitis, and they appeared to make his throat much worse. In 1953 he was given five injections of 300,000 units of procaine penicillin in two days for a sinus infection. Twelve days after the last injection large weals appeared on the ankles, thighs and legs, and he had intense pruritus. Fifteen days after the injection his tongue and larynx swelled and he had great difficulty with breathing and swallowing. The symptoms cleared after seven days, then recurred with renewed violence in spite of intensive treatment with antihistamine drugs, but the symptoms are now gradually subsiding. Skin tests in his case gave negative results.

Treatment.

It is obvious that treatment with penicillin should be stopped immediately sensitivity symptoms appear; but if sulphonamides have also been given it may be hard to decide which of the agents are causing the symptoms. In many mild cases the symptoms will clear up quickly, but in a great many they resist all forms of treatment and may persist for many weeks. Desensitization may be attempted by injection or by the oral route. I have tried oral desensitization in two cases, starting with a dose of about 100 units and doubling the dose every six hours; but although tolerance of a dosage up to about 5000 units was attained, desensitization, if ever achieved, did not seem to last and contact symptoms recurred.

Antihistamine drugs in my experience have proved disappointing; some types of reaction seem to resist all known antihistaminics, but in other cases there seems to be some subjective improvement but little objective improvement. Antihistaminics appeared to have no effect at all on giant urticaria. Adrenaline did not appear to have any effect on the serum sickness types of reaction I have seen, and ephedrine was of doubtful value. Other forms of treatment have been advocated, including the intravenous administration of histamine, vitamin *K*, vitamin *B* complex, the intravenous administration of niacin or of glucose, and the administration of staphylococcus toxoid, ACTH and cortisone. In some cases non-specific treatment by injections of gradually increasing doses of a stock mixed bacterial vaccine seemed to produce considerable relief of symptoms.

Pelner and Waldman (1952) describe very good results in the serum-sickness type of reactions with sodium dehydrocholate, a derivative of desoxycholic acid, which is the starting point of cortisone synthesis. They give five millilitres of a 20% solution intravenously every day or every other day, according to the severity of the reaction, and as well give one tablet of dehydrocholic acid (222 milligrammes) orally three times a day. They consider that ACTH, cortisone and sodium dehydrocholate mediate anaphylactic and other allergic reactions by "occupation" or depression of some of the liver functions. Freed and Lindner (1941) showed that adrenal steroids appear to reduce capillary permeability. When ACTH or cortisone has been used in the cases I have encountered, the response seems to have been good.

Summary and Conclusions.

A brief review of the symptomatology, the types of reaction, and the factors in the acquisition of penicillin sensitivity are given, and the results of skin tests in 27 cases are analysed. It is stressed that the taking of a careful history about previous injections of penicillin and any reactions occurring from them is much more important than the placing of reliance on skin tests to detect sensitization to this antibiotic.

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THE EFFECT ON GASTRIC ACIDITY OF "NULACIN" TABLETS.

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THE following report confirms the findings of Douthwaite and Shaw (1952), who reported the effects on gastric acidity produced by "Nulacin" tablets. They showed that while they were sucked, gastric acidity was greatly reduced. "Nulacin" tablets have the following composition: solids from whole milk combined with dextrins and maltose 40 grains (2·4 grammes), magnesium trisilicate 3·5 grains (0·25 gramme), magnesium oxide 2·0 grains (0·12 gramme), calcium carbonate 2·0 grains (0·12 gramme), magnesium carbonate 0·5 grain (0·03 gramme), *Olei Menthæ Piperitæ, quantum sufficit.* The tablets are one inch (2·5 centimetres) in diameter and three-sixteenths of an inch (0·5 centimetre) thick. They are placed between teeth and cheek and allowed to dissolve.

Douthwaite and Shaw designed these tablets to provide, while they were sucked, a continuous effect on gastric acidity by imitating continuous intragastric milk and alkali drip therapy. They found a striking effect in seven patients suffering from duodenal ulcer who were investigated with gruel test meals. To six of these subjects on two consecutive days they gave test meals, and during the second meal, after withdrawal of the third specimen (fifteen-minute intervals), a "Nulacin" tablet was placed between gum and cheek and allowed to dissolve. It was replaced as soon as dissolved, and three tablets were consumed in this way over the hour of sucking tested.

The results of their testing showed that during the hour in which the tablets were being sucked, free acid was completely neutralized.

Methods.

In repeating Douthwaite and Shaw's work, we have used "Nulacin" tablets given in the same way. For the test meal, instead of gruel, we have used alcohol (50 millilitres of 7% ethyl alcohol), which is a sterner challenge. Six patients with duodenal ulcer were tested—five men and one woman. In three instances the test meal examination without "Nulacin" was carried out first. In the other three the test meal examination with tablets being sucked was first performed. Throughout the test meal without tablets, saliva was swallowed. In each case the tests were carried out three to seven days apart.

Douthwaite and Shaw stated that their subjects consumed three tablets in the hour. We found that a range of 1·25 to 3·0 tablets was consumed (average 2·0 tablets) in the same period.

Results.

Table I shows the readings obtained for free and total acid, with and without tablets.

Figure I shows the composite curves constructed from averages of free acid, with and without the tablets.

From these results it is clear that while the tablets are sucked, a striking reduction of acidity occurs. Within fifteen minutes of removal of the tablet the gastric acidity rapidly rises.

[1] Sol Green Research Scholar, Alfred Hospital, 1953.

TABLE I.

Patient.	——		Sample Times in Minutes.								
			0	15	30	45	60	75	90	105	120
1. Ri.	Without "Nulacin".	Free acid[1]	68	45	52	71	66	57	52	48	58
		Total acid[1]	84	62	67	81	80	73	67	61	72
	With "Nulacin".	Free acid ..	30	61	70	70	0	0	0	0	37
		Total acid ..	75	86	81	78	12	20	17	13	63
2. An.	Without "Nulacin".	Free acid ..	67	71	68	63	51	40	41	36	32
		Total acid ..	76	80	81	73	60	53	52	47	42
	With "Nulacin".	Free acid ..	68	67	70	73	0	0	28	19	57
		Total acid ..	80	76	82	81	10	6	46	33	63
3. Go.	Without "Nulacin".	Free acid ..	60	49	76	76	76	55	64	65	64
		Total acid ..	75	62	89	89	87	67	76	78	77
	With "Nulacin".	Free acid ..	38	32	43	52	0	0	0	0	57
		Total acid ..	47	42	53	60	8	7	21	25	73
4. Sl.	Without "Nulacin".	Free acid ..	36	37	14	36	50	43	62	49	46
		Total acid ..	53	42	33	48	62	58	77	64	58
	With "Nulacin".	Free acid ..	40	45	51	44	5	7	4	3	10
		Total acid ..	55	55	58	54	15	15	7	6	27
5. Hi.	Without "Nulacin".	Free acid ..	0	0	0	15	53	37	47	60	42
		Total acid ..	9	9	6	27	66	50	57	72	50
	With "Nulacin".	Free acid ..	0	0	24	37	0	0	0	10	55
		Total acid ..	19	11	37	50	14	8	7	26	69
6. Le.	Without "Nulacin".	Free acid ..	0	41	70	81	49	59	50	46	50
		Total acid ..	13	51	85	92	64	71	62	58	63
	With "Nulacin".	Free acid ..	28	52	82	55	37	0	0	0	0
		Total acid ..	45	61	94	70	48	10	9	9	9

[1] Clinical units.

Summary.

Six patients with duodenal ulcer were tested with "Nulacin" tablets, which were sucked throughout one hour of an alcohol test meal, and the results were compared with those obtained from an alcohol test meal examination of the same subjects when no tablets were given. The results confirm Douthwaite and Shaw's finding of a striking reduction in gastric acidity while the tablets were being sucked.

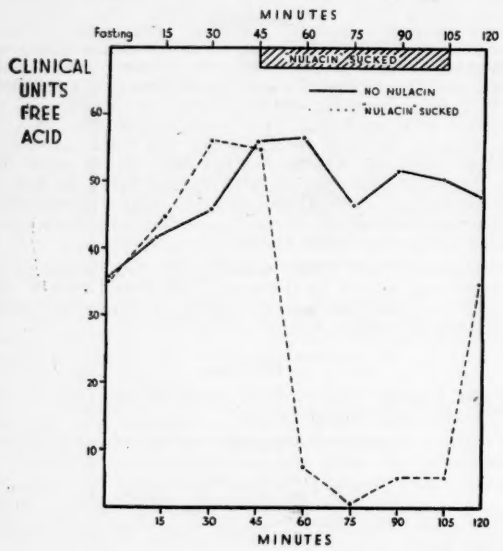

FIGURE I.

Average free acid curves (alcohol test meals) of six patients with duodenal ulceration, with and without "Nulacin".

Reference.

DOUTHWAITE, A. H., and SHAW, A. B. (1952), "Control of Gastric Acidity", *Brit. M. J.*, 2: 180.

Reports of Cases.

REPORT OF A CASE OF ALEUCHÆMIC MYELOID LEUCHÆMIA AND PREGNANCY.

By EVA A. SHIPTON,
Sydney.

LEUCHÆMIA associated with pregnancy is not common; but with the increase in leuchæmia which is apparently world wide (Sachs and Seiman, 1947; Heilmeyer, 1951), this association may be expected to increase and the treatment and prognosis to assume greater importance.

Routine full blood counts when women report for the first pre-natal examination, and also during pregnancy, will bring to light cases which would otherwise have been missed, and definite information will be obtained as to whether the pregnancy is occurring in the course of leuchæmia or whether the leuchæmia has commenced during the pregnancy. The practice of estimating only the hæmoglobin value is to be avoided.

Clinical Record.

Mrs. R. was examined at the Mater Misericordiæ Maternity Hospital on April 11, 1949; she was pregnant for the second time. Her last menstrual period had occurred on October 18, 1948. No abnormality was detected in the physical examination. The patient gave a history of having had a cyst removed from the left ovary in 1947. On August 16, 1949, a healthy living female child was born, and on August 24, 1949, the patient was discharged from hospital without further comment; there is no record of a blood examination.

On June 26, 1950, she reported again, when she was approximately five months pregnant, not having menstruated since before the birth of the previous child. No abnormality was detected at the first examination, and she was sent for the routine blood count on July 7, when the diagnosis of aleuchæmic myeloid leuchæmia was suggested. A further blood count after two months showed deterioration of the condition, and the patient was given "Fersolate" and a blood transfusion. Physical examination failed to reveal any enlargement of glands, liver or spleen at any stage of the disease.

The results of blood counts during the following months can be seen from Table I. The patient was given a further transfusion on October 6, and on October 20 she was delivered of a living female infant, after a normal labour, without excessive hæmorrhage. This child has remained well and developed normally. The patient died ten months later.

TABLE I.

Date.	Hæmoglobin Value. (Grammes *per Centum*.)	Red Corpuscles per Cubic Millimetre.	White Cells per Cubic Millimetre.	Myeloblasts. (Percentage.)
7. 7.50	12·6	3,600,000	7,000	3·0
6. 9.50	8·6	2,700,000	6,200	6·0
14. 9.50	10·8	3,200,000	8,000	10·5
17. 9.50	(Transfusion)			
18. 9.50	11·4	3,300,000	10,000	24·0
25. 9.50	9·8	2,800,000	9,600	18·0
3.10.50	8·1	2,600,000	8,000	6·0
6.10.50	11·4	2,400,000	7,800	—
	(Transfusion)			
9.10.50	13·8	4,200,000	8,000	11·0
16.10.50	12·9	3,800,000	8,000	—
20.10.50	13·6[1]	4,100,000	14,000	—
23.10.50	10·0	3,200,000	12,000	—
27.10.50	(Transfusion)			
14.11.50[2]	12·4	3,600,000	3,600	2·0
10.8.51[3]	1·8	888,000	18,000	92·0

[1] Just after confinement.

[2] From this date blood counts were made frequently until the patient's death, and did not show any notable changes.

[3] Final count, two days before the patient's death.

Comment.

The type of leuchæmia least likely to interfere with conception and pregnancy is the chronic myeloid type. This can be explained by the fact that patients in the older age group are usually affected by the lymphatic type (Heilmeyer, 1951), and by the fact that histologically the ovaries, uterus and endometrium are more densely infiltrated by the lymphatic cells than by the myeloid cells (Nevinny-Stickel, 1948).

In two examples of pregnancy in chronic lymphatic leuchæmia on record, the diagnosis is questionable; the third appears to be authentic (Stodtmeister and Webb, 1944). There are reports of acute lymphatic leuchæmia with pregnancy; but in some of these cases sufficient evidence is not available to state whether the type cell is myeloblastic or lymphoblastic.

Two cases of monocytic leuchæmia in pregnancy are on record; but in the majority of recorded cases of pregnancy and leuchæmia the leuchæmia is of the chronic myeloid type, and there are several accounts in the literature of more than one pregnancy during the course of the disease (Laubenberg, 1891).

The question of the advisability of interference with pregnancy in these cases has been discussed since 1901 (Herman). Saidl (1931) stated that leuchæmia was an indication not only for the prevention of pregnancy, but also for its interruption.

Neumann (1928) believed that during the first two years of the disease completion of pregnancy was not of great danger to mother or child; later in the disease the danger increased, and in cases of acute leuchæmia interruption of pregnancy was advised only when the possibility existed of saving a viable child. He finally (1930) strongly advocated sterilization in chronic cases.

Grier and Richter (1939) concluded that interference with pregnancy did not help the mother in any form of leuchæmia; it only tended to produce premature or non-viable babies, and in the acute form it shortened the mother's life.

Tschopp (1939) reports an instance in which interference with a second pregnancy in the fifth month in a woman suffering from chronic myeloid leuchæmia changed the blood picture to the acute myeloblastic type with a fatal outcome.

The advisability of Cæsarean section for these patients is not upheld by a study of the literature.

Moloney (1945) reported a successful result in a case in which the mother suffered also from preeclamptic toxæmia. In Applebaum's case (1944) of acute myeloid leuchæmia, the Cæsarean section at seven and a half months resulted in a still-born infant and the death of the mother several hours later. In spite of the hæmorrhagic diathesis frequently associated with leuchæmia, death of the mother from hæmorrhage is rare.

Lazarus and Fleischmann (1905) reported the case of a patient with acute myeloid leuchæmia who died of hæmorrhage after a spontaneous abortion at the fifth month, and Geller's (1929) patient died of hæmorrhage two hours after a Cæsarean section. Saidl's (1931) second patient died of hæmorrhage after a spontaneous abortion at the seventh month.

There is no record of a leuchæmic mother giving birth to a leuchæmic child.

Although mouse leuchæmia can be transmitted by inoculation of leuchæmic blood, Burchenal (1940) was unable to show transmission of the disease from mother to offspring.

The interesting work of Dobberstein and Seifried (1938) on leuchæmia in domestic animals has shown that in cattle lymphadenosis is much more frequent than myelosis and that the disease can be transmitted to the young through the placenta. This is of great interest if leuchæmia is regarded as a viral disease, and Kucharick (1940) has discussed this aspect fully.

Erf (1947) made an extract from the placenta of a patient suffering from myeloid leuchæmia, injected it into guinea-pigs, and produced myeloid cell infiltrations in the organs which he failed to obtain with a similar extract of a normal placenta.

Reports on the microscopic examination of the placentas from leuchæmic women are not numerous. Askanazy (1894) showed that there was no intermingling of the leuchæmic blood of the mother and the normal blood of the fœtus, and this was confirmed by Ohlsson (1925).

The increasing number of reports of familial leuchæmia stress the need for careful follow-up reports of all children of leuchæmic mothers.

The study of leuchæmia in pregnancy shows that interruption of pregnancy is contraindicated, and that with supportive treatment, which includes blood transfusions, a live child can be obtained in the majority of cases and the life of the mother not further endangered. The facts that spontaneous remissions do occur in leuchæmia (Berge, Jenks and Davis, 1949), and that at times diagnosis may be difficult, support this conclusion.

Summary.

A case of aleuchæmic leuchæmia with pregnancy is reported, some of the literature is discussed, and the conclusion is reached that with modern methods of treatment interruption of the pregnancy is contraindicated.

Acknowledgements.

I have to thank Dr. R. B. C. Stevenson and Dr. F. H. Hales Wilson for the clinical notes of this patient, and the Royal Society of Medicine for photostat copies of the literature unavailable here.

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Reviews.

Biologie, Pathologie und Therapie der Gelenke dargestellt am Kniegelenk. By Arnold Sonnenschein, M.D., D.Ph.; 1952. Basel: Benno Schwabe and Company. 10" x 7", pp. 508, with 219 illustrations. Price: Swiss francs, 54.10.

DR. ARNOLD SONNENSCHEIN has written a magnificent volume on the clinical and therapeutic aspects of joint disease as presented in the knee joint. The author's style is concise and lucid.

This book is a comprehensive concept of present-day opinion on this subject; it is especially suitable for those preparing for a career in the study and treatment of some department of joint disease. The specialist will find the repeated mention of standard details rather irksome, but even he will be surprised by the learning and industry of the author.

There are 17 pages of closely printed references, and for these alone the student or practitioner would find the book worth buying. *Actually in our opinion the book will last as* a model and a classical clinical monograph.

A careful dissection of Sonnenschein's references shows a scant knowledge of English clinical arthrology. American joint literature has been well scanned. It is worthy of comment that of the one author who has classified his principles into ten concepts—H. O. Thomas—no mention is made. There is no evidence of reliance on principles so clearly stated by the English school of the last century.

Where an English surgeon would have a specific test for union of a fracture or healing of a ligament, as taught by Thomas, the Viennese school sets down a generality. Apparently, there is still much room, or indeed necessity, for a commingling of the learning of the various nations.

The chapter on "Acquired Deformities and Functional Knee Lesions" is excellent and enriches our perhaps lax codification of these lesions. Here, the author considers principles and brings in the specific lesions as exemplars. The chapter includes "Genu laxum, Genu paralyticum, Genu precipitans, Contractura Genus and Ankylosis Genus". "*Genu precipitans*" is a tidy concept and includes all those lesions which give rise to snapping knee joint. The chapter on this subject is very well written and stresses the important point that, in the range of extension from 160° onwards, the ligaments of the knee are tense and clamp down hard on any inequalities between articular surfaces. Here, one has to admire the detail of therapy as given. The physiotherapy details make one realize that physiotherapy is taken most seriously in Austria; perhaps we could, with advantage, imitate Sonnenschein and his friends in this regard.

One point in the book, which we missed, was a clear and stressed warning on the danger of lengthening a contracted *tendo Achillis* when the quadriceps is paralysed. It is a scandalous procedure, still seen now and again in Australia.

Australian physicians and surgeons are not likely to agree with an observation period of three to four years with electrotherapy in the treatment of poliomyelitis. Although the author shows a tender regard for patients' pockets, he does not appear to blush at this unnecessarily long period of therapy. The Anglo-American schools, too, will pale somewhat at the use of an ankle manschette for traction to prevent or relieve a knee flexion deformity. The author is well aware of the danger of tibial dislocation in traction of this sort, but no clear warning is given. Indeed, his fondness for anklet direct traction makes one suspect that the Viennese school is not so afraid of this complication as are we. Also, the well-known synopsis of the end results of flexion deformity of the knee could be mentioned more lucidly and explicitly, that is to say, tibial flexion, dislocation, external rotation and valgus deformity. Be it noted, however, that these things are known to him—it is only that we consider a teaching manual ought to present some highlights as "red lights", that we stress these points.

The author constantly stresses prophylaxis of deformities and complications. As an instance of his enthusiasm in this matter, he advises the cutting of a hole in a knee plaster so as to be able to exercise passive movements of the patella from side to side. Those who follow the Thomistic way of articular therapy will not agree with his frequent advice to use passive movements in convalescent stages.

Operative details are adequately described. The surgeon is presented with an historic galaxy of choice at times—as in descriptions of knee arthroplasty.

The descriptions of joint pathology are real and delightful highlights of this book. They make it a worthy descendant of the Virchow school. Throughout the book, the author discloses a very Anglo-American fear of sepsis in all his operative procedures.

Sonnenschein is enthusiastic on the modern treatment of tuberculous joints and considers that even these joints offer some opportunities for arthroplasty. At the present, perhaps not many English surgeons will agree with this opinion, although it seems we are beginning to regard joint tuberculosis as we regard other forms of joint infection, armed as we are with fairly reliable antibiotics.

It is surprising that, in the discussion of knee contusions, the very common sequel of patellar chondromalacia is not mentioned. The use of autogenous blood to produce fibrosis for healing of ligamentary tissues will, perhaps, be new to most of us, but the idea seems acceptable. It is pleasing to note *meniscus hypermobilis* stressed as a working diagnosis—a solace to the occasional "negative" meniscus exploration. Most of us are agreed, however, on the actuality of this lesion.

The discussion on old patellar fractures, a point the experienced surgeon eagerly looks up, is weak. One will not learn from the book how to treat an old fracture (say, with fragments three inches apart). However, we admire the Viennese school's conservatism in the treatment of patellar fractures, and we do not resent the fact that removal of the patella would appear to be an uncommon event in Austria in the treatment of fractures of this bone. As the place of patellectomy is not yet quite defined, the Viennese school is treading warily in this regard.

The chapter on injuries of the knee joint is beautiful. The concept of *distorsio genus*, including injuries to the collateral ligaments, the cruciate ligaments and the menisci could well be introduced into our terminology. The author has a genius for elaboration of principles which enlarge our comprehension of a complex subject.

The discussion of the maladies of the knee joint is comprehensive, and it is submitted that not much improvement will be suggested by Anglo-American surgeons on the author's classification of the arthritides. The therapeutic discussion is sane and well balanced.

Therapeutically, one will find this book a rich source of reference. The early chapters are a complete and revealing introduction to a complex study. Without wishing to be repetitive, we hope that this book will find its way onto the shelves of all interested surgeons and we look forward to an early translation into English.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Ophthalmologic Diagnosis", by F. Herbert Haessler, M.D.; 1953. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 9" × 6¼", pp. 398, with 151 text figures. Price: 85s.

The author has tried to select from the literature ophthalmological data necessary for diagnosis and to arrange them in a form in which they will be clinically useful.

"British Medical Science and Practice: An Anthology", edited by G. F. Petrie, M.D.; 1953. London: Longmans, Green and Company. Melbourne: Longmans, Green and Company, Limited. 8½" × 6", pp. 188, with 22 illustrations. Price: 25s.

Written to give an insight into the trends of British medicine with reference to ten of its pioneers, together with aphorisms and extracts from the writings of British doctors.

"Storming the Citadel: The Rise of the Woman Doctor", by E. Moberly Bell; 1953. London: Constable and Company, Limited. Sydney: Walter Standish and Sons. 8½" × 6", pp. 200, with seven illustrations. Price: 18s.

Written at the suggestion of the Dean and Governors of the Royal Free Hospital School of Medicine.

"Surgery of Trauma", edited by Warner F. Bowers, A.B., B.S., M.D., M.S., Ph.D. (Surg.), with forewords by Melvin A. Casberg, M.D., and Surgeons General of the United States Army, the Navy and the Air Force; 1953. Philadelphia: J. B. Lippincott Company. Sydney: Angus and Robertson, Limited. 10" × 7", pp. 630, with 284 illustrations. Price: £8 1s. 3d.

Comprises 28 chapters, divided into four sections, by 42 contributors.

"Clinical Unipolar Electrocardiography", by Bernard S. Lipman, A.B., M.D., and Edward Massie, A.B., M.D., F.A.C.P.; Second Edition; 1953. Chicago: The Year Book Publishers, Incorporated. 8" × 5½", pp. 310, with 260 illustrations. Price: $6.50.

The first edition was published in 1951.

"Modern Trends in Urology", edited by E. W. Riches, M.C., M.S., F.R.C.S., with a foreword by The Lord Webb-Johnson, K.C.V.O., C.B.E., D.S.O., T.D., M.B., LL.D., F.R.C.S.; 1953. London: Butterworth and Company (Publishers), Limited. Sydney: Butterworth and Company (Australia), Limited. 10" × 7", pp. 490, with 215 illustrations. Price: £5 2s. 6d.

Contains 38 chapters on different subjects by various authors, most of whom are British.

"Advances in Pediatrics", edited by S. Z. Levine, with associate editors John A. Anderson, Margaret Dann, L. Emmett Holt, junior, A. Ashley Weech and Myron E. Wegman; 1953. Chicago: The Year Book Publishers, Incorporated. Volume VI. 9" × 6", pp. 324, with about 50 illustrations. Price: $7.50.

Deals with seven different subjects by different authors and groups of authors.

"Carcinoma of the Female Genitalia" by Hans Ludwig Kottmeier, M.D.; 1953. Baltimore: Published for Vanderbilt University by The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 8½" × 5½", pp. 224, with 59 illustrations. Price: £2 5s. 9d.

This is number seven of the Abraham Flexner series of lectures.

The Medical Journal of Australia

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All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: surname of author, initials of author, year, full title of article, name of journal without abbreviation, volume, number of first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

THE HYPODERMIC INJECTION OF MORPHINE FOR THE RELIEF OF PAIN: A CENTENARY.

ON November 28, 1853, the first hypodermic injection of morphine for the relief of pain was given by Dr. Alexander Wood, lecturer on preventive medicine. This fact is recorded in the *Edinburgh Medical and Surgical Journal* of April 1, 1855, Volume LXXXIII, page 265.[1]

Wood begins his article by stating that an immense improvement was effected in the treatment of neuralgic disorders when Valleix directed attention to the fact that while on the one hand the superficial nerves of the body were, of all others, those most commonly affected with neuralgia, there were some points of their course in which it was much more liable to be seated than in others, although in these no structural alteration could be discovered to account for the liability. He quoted Valleix as having stated that the points in the course of any nerve which were liable to be the seat of tenderness were: (*a*) the place of emergence of the nerve trunk, (*b*) the point where a nervous twig travelled to muscles to ramify on the integuments, (*c*) the point where the terminal branches of a nerve expanded in the integuments, (*d*) the point where the nervous trunks became superficial during their course. Wood observes that it is scarcely necessary to remark that all these points are precisely those at which the nerve tends towards the surface, and therefore where, of course, it is most amenable to local treatment. Valleix, acting on his observations, introduced a plan of treatment which as an external remedy Wood had largely employed ever since his attention was first directed to Valleix's work in 1842. This treatment consisted in the application of a succession of small blisters over the points in the course of the nerves which were painful on pressure. Valleix did not recommend, as a general rule, the application of morphine endermically, but suggested that it might be attempted with advantage in some cases. Wood states that he had almost invariably employed an ointment containing morphine to dress the blistered surface, and had been accustomed to ascribe much of the benefit of treatment to this procedure. In some cases, he had seen relief follow the application of an ointment containing strychnine to the blistered surface, but he adds that this had to be used with great caution and that very disagreeable results often ensued from its use. Wood states that it had frequently occurred to him that a more direct application of the narcotic to the affected nerve or to its immediate neighbourhood would be attended with corresponding advantage, and as the painful points so often corresponded to those in which the nerve became superficial, he thought that this might be accomplished. In pursuit of this object, he had several times made attempts to introduce morphine directly by means of acupuncture needles and otherwise, but without success. At the end of 1853, he had occasion to try to remove a nævus by injection with the acid solution of perchloride of iron, and he procured for this purpose "one of the elegant little syringes" constructed for the purpose by Mr. Ferguson, of Giltspur Street, London. While he was using this instrument for the nævus, it occurred to him that it might supply the means of bringing some narcotic to bear more directly than he had hitherto been able to do on the affected nerve in neuralgia, and he decided to make the attempt. He describes the history of an old lady who had long laboured under gastric and nervous symptoms and had suffered severely for four days from cervical brachial neuralgia. This patient had an idiosyncrasy against the taking of opium. She had been warned about this before she came under Wood's care, and consequently he had never prescribed it for her. On November 28, at 10 o'clock p.m., he visited the patient in order to give her an opiate for the night. Having ascertained that the most tender spot was the post-clavicular point of Valleix, he inserted the syringe within the angle formed by the clavicle and acromion and injected 20 drops of a solution of muriate of morphine of a strength about double that of the official preparation. Ten minutes after withdrawal of the syringe the patient began to complain of giddiness and of confusion of ideas; in half an hour, the pain subsided and Wood left her in the anticipation that she would have a refreshing sleep. He saw her again at about 11 o'clock a.m. on the morning of the 29th, and was a little annoyed that she had not awakened; the breathing was somewhat deep and she was roused with difficulty. After the use of energetic stimuli, the symptoms disappeared and from that time the neuralgia had not recurred. Wood quotes other cases in which he injected opiates.

In discussing the *modus operandi* of "this new application of remedial means" Wood states that medicines when exhibited have usually two effects. The first is a local or topical effect on the tissue to which it is applied; the second are remote effects, being physical, chemical or vital changes produced on parts at a distance from those to which the medicine is directly applied or on the system at large. The way in which the local effect is produced is, he states, comparatively simple and depends on the relation of the medicine to the tissue to which it is applied. Some applications simply stimulate or irritate tissues, the effect

[1] We are indebted to Dr. C. E. Corlette, of Sydney, for a transcript of this article.

varying from the least powerful which merely produces redness, to the most powerful which may produce gangrene. Others form compounds with the elements of the tissue, thus chemically decomposing or corroding it, while a third class, according to Christison, "neither corrode or irritate, but *make a peculiar impression on the sentient extremity of the nerves, unaccompanied by any visible change of structure*". In regard to the way in which remote effects are produced, Wood states that considerable difference of opinion prevails. Magendie and his supporters contended that the drug was conveyed by absorption from the part to which it was applied, and others, such as Morgan and Addison, were of the opinion that the remote effects were exclusively due to sympathy or to an impression transmitted through the nerves. Others were unable to adopt either view exclusively, but admitted a double method of operation. We need not follow Wood in his discussion of these views. He states that he himself was engaged in these experiments in which various substances had been introduced into the cellular tissue with comparatively little injury to the adjacent vessels, and as far as his observations had gone, they had led him to ascribe great absorbent power to the cellular tissue. He regarded it as proved that (*a*) medicines are more rapidly absorbed by some tissue than by others; (*b*) that the stomach is by no means the most rapid way of introducing medicines into the system; and (*c*) that the cellular tissue has a great power of absorption.

It must suffice to quote Wood's important conclusions which he draws from the cases reported by him. They are as follows:

1. That narcotics injected into the neighbourhood of the painful point of a nerve affected with neuralgia will diminish the sensibility of that nerve, and in proportion, diminish or remove pain.

2. That the effect of narcotics so applied are not confined to their local action, but that they reach the brain through the venous circulation, and there produce their remote effects.

3. That in all probability, what is true in regard to narcotics would be found to be equally true in regard to other classes of remedies.

4. That the small syringe affords a safe, easy, and almost painless method of exhibition.

5. That destitute as we are of any precise experiments as to the applicability of cellular tissue as a medium for the reception of medicinal agents, the experiments made with the syringe show that it seems to offer an excellent surface for the absorbent action of the venous system.

6. That the method now detailed seems as extensively applicable as any of the methods of applying remedies to the skin, whether enepidermic, iatraleptic, endermic, or by inoculation.

It gives us pause to remember that it is only one hundred years since drugs have been given by hypodermic inoculation. Alexander Wood was one of the great benefactors in clinical medicine, and it is appropriate that his work should now be remembered.

THE BACKWOODS PHYSIOLOGIST.

ONE HUNDRED YEARS ago, in April, 1853, there died in St. Louis an American physician who, under the most unfavourable circumstances, made a classical series of observations that form, in the words of Frederick Stenn,[1] the basis of modern gastric physiology. This was William Beaumont, an illustrious figure in the history of American science and indeed in the history of medical science generally; yet it is probably true to say that his name is less known in this country than that of the subject of his experiments, Alexis St. Martin. It would be hard to find a finer example of those who achieve greatness than Beaumont, or a more striking example of those who have greatness thrust upon them than St. Martin. This can be best brought out by quoting two men who are themselves great in their own right. The physiologist Walter B. Cannon[1] writes of Beaumont:

Having none of the opportunities for conference and sympathetic discussion with fellow workers; having, indeed, no scientific companions, no library, no journals, no chance of consulting experts in any difficulty, and possessing no laboratory equipment except a thermometer and a few vials, he prosecuted researches on the gastric juice and the gastric digestive processes which have never failed to evoke admiration from all who have read his record. And because he respected "the true spirit of inquiry" and "honestly recorded the result of each experiment as it occurred", his labors, despite the privations he suffered, were fruitful and had influence far beyond the boundaries of his own country, in France, Germany, and Russia.

Sir William Osler[2] writes of Alexis St. Martin:

On June 22, 1822, the accidental discharge of a musket made St. Martin, a *voyageur*, one of the most famous subjects in the history of physiology, for the wound laid open his stomach, and he recovered with a permanent gastric fistula of an exceptionally favourable kind.

The accident occurred at Fort Mackinac in Michigan, where William Beaumont was fort surgeon; and at Fort Mackinac St. Martin stayed until he absconded in 1829 to return to his relatives in Lower Canada. Beaumont persuaded him to return, and a second, third and fourth series of observations were made and recorded. The whole experimental period was, according to Osler, from August 1, 1825, to November 1, 1833. Stenn tells us that Beaumont performed several hundred experiments, which were often fatiguing to Alexis, who was obliged to lie in one position for long periods of time. But the union of Alexis's patience and Beaumont's "fiery enthusiasm" had a noble issue. Stenn summarizes it thus:

The great physiologist had proved what others thought they had discovered a century later, that the stomach juices are formed in the walls of the stomach; through a hand lens he saw the juices collecting at the orifices of the glands in the mucous membranes, the juices appearing only with the stimulation of food. . . . He distinguished gastric juice from saliva and mucus present in the stomach. He found that gastric juice is acid and that its digestive property is due to something besides acid. . . . As the quantity of food is increased, the formation of gastric juice is enhanced. Beaumont also studied the time of digestion of different types of foods and noted how oils and fats retard stomach emptying and how starches pass from the stomach more rapidly than other foods. He observed the contractions of the body of the stomach at the beginning and those of the pylorus at the end of digestion. The manner in which hunger is relieved by the insertion of food directly into the lumen of the stomach and the way gastric secretion is suppressed or absent in states of anger, impatience, and fever, are his classical discoveries.

There must be few finer achievements in medical science than the work of this "backwoods physiologist", as Osler called him, and we do well to honour his memory. Moreover, he must not be thought of as a callous experimenter or the bullying exploiter of a reluctant human guinea-pig. He is known to have been "a beloved practitioner with a

[1] *J.A.M.A.*, July 4, 1953.

[1] "The Way of an Investigator", 1945, page 44.

[2] "The Army Surgeon", in "Æquanimitas", Lewis, 1904, page 119.

wide following, revered for his noble character by his fellow physicians, and a devoted father and husband", and the long-suffering Alexis seems to have needed only a little persuasion to return for the three later series of experiments. However this may be, Beaumont's standards of experiment, observation and recording are in the highest traditions of science; his own splendid words sum them up: "Truth, like beauty, 'when unadorned is adorned the most', and in prosecuting experiments and inquiries I believe that I have been guided by its light." Such is the ideal and such is the faith of the frontiersman in science, comments Cannon, "and in so far as he is loyal to his convictions he will leave behind him, as Beaumont did in his records, lasting contributions from his fleeting years".

Current Comment.

MULTIPLE MYELOMA.

A NUMBER of interesting features of plasma cell myelomata—perhaps better referred to as multiple myelomatosis, as being less dogmatic in regard to the cell type—are reviewed in a survey by G. C. Meacham of 51 cases diagnosed at the University Hospitals of Cleveland.[1] The clinical course is not discussed in detail, but, as is well known, the common presenting features are anæmia and bone pain, less commonly pathological fractures, root pain and uræmic manifestations. Somewhat commoner in males in most reported series, its onset is rare before the fourth decade.

Anæmia of some degree is almost invariably present, but Meacham found in his series that in 22 of 29 cases in which mean corpuscular volumes were determined the cell size was greater than 95 cubic microns. He emphasizes the fact that patients may be referred with the diagnosis of pernicious anæmia resistent to treatment. It is possible that the absolute estimations were made only in cases in which a high colour index was present, so that the proportion of cases associated with a macrocytic anæmia appears deceptively high. Although plasma cells were found in the peripheral blood in 16 cases, the value of bone marrow biopsy in establishing the diagnosis conclusively was undoubted. This gave unequivocal results in 39 out of 41 instances in which it was performed (either by aspiration or surgical biopsy). Although in both the remaining cases only a slight increase in plasma cell content of the aspirated specimen was present, the cells were immature and the other findings left no doubt about the diagnosis. Radiologically, some abnormality of bone was demonstrated in 96% of cases, in most of which discrete translucent areas were associated with diffuse osteoporosis, only 20% having the typical "punched-out" areas alone. More significant, however, is the fact that in seven patients no more than a diffuse osteoporosis was present. This, in a patient presenting with bone or perhaps nerve root pain, may constitute a diagnostic trap, and Meacham remarks in this regard that senile osteoporosis rarely involves the skull. In three cases no radiological abnormality was found. The serum globulin content was above 4·0 grammes per 100 millilitres in more than half the cases, and more than 3·0 grammes per 100 millilitres in nearly three-quarters of the series. There was no correlation between the marrow plasma cell content and the globulin level. Most patients with a high globulin level had no Bence-Jones protein in the urine, proteinuria being present more commonly when the globulin levels were within the normal range. Impaired renal function was present in a significant number of those with Bence-Jones proteinuria: it follows that the globulin content was usually less than 4·0 grammes per 100 millilitres in cases in which renal involvement was apparent. Hypercalcæmia (present in 25% of the series) was found in seven of the 13 cases with definite "nephritis", the ionized calcium level being consistently high also in this group. Meacham points out that it is unusual for this to occur in cases of renal damage irrespective of cause. He does not discuss the clinical manifestations of the renal lesions in detail, but it is indicated that in his cases the chief features were nitrogen retention and albuminuria in the presence of a relatively normal blood pressure.

The brief consideration given to treatment reflects our inability to influence significantly the course of this disease. Urethane is of undoubted value in the symptomatic relief of pain. Meacham has found no benefit from cortisone and ACTH, with the exception of one patient who developed hæmolytic anæmia which responded to the latter.

Apart from the suggestion that the excess ionized calcium may combine with the Bence-Jones protein to form a more than usually tenacious cast leading to renal damage by tubular obstruction, Meacham makes no claim to have added to our understanding of the condition. Nevertheless, his is an interesting paper on an interesting if depressing disease. One aspect which Meachem does not emphasize, but which was reviewed by David Cowling[1] in a paper in this journal two years ago, is the variable histopathological changes which may be found. Three of his eight cases were not of the typical plasma cell type, and Cowling concurs with Robb Smith's classification which places multiple myeloma with the reticulosarcomata. Any disease classified in this group because of its lack of uniformity is a challenge to pathologist and clinician alike.

[1] *Ann. Int. Med.*, May, 1953.

PHYSIOLOGICAL OBJECTIVES IN HOT WEATHER HOUSING.

FOR untold thousands of years man has employed energy to warm his domestic environment when that was necessary; it is just as logical to use energy to cool the domestic environment when the outside temperatures are high, but this procedure demands engineering complexities and is limited at present to wealthy institutions and to those few persons whose incomes are exceptionally large. The very practical problem arises of how by housing to protect the dweller against the physical stresses of hot climates without commitment to expensive central cooling devices. Professor Douglas Lee made good use of his opportunities when holding the chair of physiology in Queensland and directed his research towards the action of tropical climates on the white man. Nowhere in the world could this important inquiry be conducted under such favourable circumstances, for tropical Australia is reasonably free from the more serious tropical diseases, there is no large native population to act as a reservoir of infection and, as there are no coolies, all types of physical work are conducted by white men and women. It is good that Professor Lee seized this opportunity when it presented, especially when well-intentioned efforts elsewhere were rendered nugatory by official action. Now professor of physiological climatology in the Johns Hopkins University, he has produced a brochure on physiological objectives in hot weather housing.[1] In it he gives first of all a preliminary survey on the physiology of animal heat with particular reference to the human body. There is much original matter in this reconnaissance, and the teacher of physiology, no matter how well versed in this branch of the subject, should read the exposition carefully. Then comes a lively presentation of the varieties of hot climates which the human body can encounter on the surface of the earth, with special regard to insolation, infra-red reflection, temperature, humidity, wind movement and all factors which influence heat loss from skin and lungs as well as heat gain from the environment.

[1] M. J. AUSTRALIA, May 5, 1951.

[2] "Physiological Objectives in Hot Weather Housing: An Introduction to the Principles of Hot Weather Housing Design", prepared by Douglas H. K. Lee, under a contract with the U.S. Department of State Technical Cooperation Administration Institute of Inter-American Affairs; 1953. Washington: United States of America Housing and Home Finance Agency. 10¾" × 8", pp. 90, with 15 illustrations. Price: 45 cents.

Professor Lee reminds us that a simple classification of climates according to latitude cannot fail to give rise to errors of considerable magnitude, and so presents us with a climatic survey which is admirably designed. He might have gone further and pointed out that characteristic vegetation is a sure criterion; for example, coconut palm climate and date palm climate represent two very different sets of conditions, which would require lengthy treatment were they to be described in meteorological terms. A large part of the publication is occupied with suggestions concerning the architecture of houses and other buildings. Such considerations as height of ceiling, ventilation above and below, insulation, east-west orientation, the special types of surface needed at different positions in the building, shade trees, outside blinds and a number of other details are all explained scientifically with the aid of diagrams, many of which have a humorous appeal. This brochure covers the chosen scope of the inquiry exceedingly well and can be warmly recommended.

THE ASSESSMENT OF RESPIRATORY FUNCTION.

SOME of the difficulties in assessing respiratory function, with special reference to the role of vital capacity estimations, were noted in these columns a year ago.[1] The publication of a series of papers delivered at a meeting of the Section of Experimental Medicine in the Royal Society of Medicine[2] dealing comprehensively with this problem provides a suitable occasion for renewing the discussion. For assessing overall function, as C. B. McKerrow pointed out, three tests are in common use—the vital capacity, the maximum breathing capacity and the mean expiratory flow rate. The first of these was critically examined in the earlier "Current Comment": briefly, it is relatively insensitive, is not closely related to clinical observation of exercise tolerance, and takes no account of respiratory rate. On the other hand, it is simply and quickly performed. The maximum breathing capacity, measured over fifteen seconds, is theoretically more satisfactory, but it is time-consuming and requires a cooperative patient. Wide variations are found in the normal ranges reported by different observers, partly owing to variations in technique and errors due to the apparatus. More important, however, is the influence of air flow resistance in the system upon the result, the maximum breathing capacity decreasing with increasing resistance. It is unlikely, therefore, that comparable results will have been obtained from any two centres to date, but suitable methods incorporating low resistance circuits are described by McKerrow. The expiratory flow rate estimation, made over the first 0·75 second of a single maximum expiration, is obviously a very simply and quickly performed test requiring no great cooperation on the part of the patient, who may indeed be severely disabled at the time of the test without affecting its validity. M. C. S. Kennedy[3] describes this test in some detail in the ensuing discussion, but for full details the reader should refer to his major paper[3] in which the theoretical basis is discussed and statistical aspects are presented. There is an extremely high correlation between the expiratory flow rate and the maximum breathing capacity, so that it is doubtful whether the more elaborate test offers any additional information, at least in normal subjects and in patients with emphysema or pneumonokoniosis, groups which have so far been most intensively studied. In passing, it may be noted that information useful to the clinician has been obtained by using this test to reflect changes in bronchial diameter, Kennedy and J. C. P. Stock[4] demonstrating the bronchodilator action of khellin by this means. Stock and Kennedy[5] have also used it in the assessment of disability of patients with mitral stenosis.

McKerrow indicated the means available for studying respiratory mechanics. These are at present chiefly of interest to research workers, but the factors involved may be noted. Thus, facilitating inspiration, there are the muscular force of the diaphragm and intercostals and the elastic recoil of the chest wall tending to increase its volume; opposing inspiration are the elasticity of the lungs, a viscous resistance on the part of the chest wall and lungs to deformation and the viscosity of the air flow through the air passages. The total force available may be estimated by measuring the maximum inspiratory and expiratory pressures reached by sucking and blowing against a mercury manometer.

D. V. Bates[2] outlined the tests available for assessing gas distribution within the lungs and the efficiency with which the blood is ventilated. These again are research techniques, at least in this country, and it must suffice to give brief examples of the information which may be obtained. There is a slightly uneven distribution of air within the lungs, as shown by gas-mixing studies in normal people particularly with advancing years, but the distribution becomes grossly uneven in asthmatics even in the absence of clinical evidence of bronchospasm or emphysema, in which disease, of course, there is gross disorder of distribution. If gas-mixing studies are combined with study of the efficiency of blood ventilation—based on observations of carbon monoxide uptake—then some idea of blood distribution within the lung and of the state of the alveolar membrane may be obtained.

Thus, the uneven air distribution in uncomplicated asthma is accompanied by some redistribution of blood flow, the poorly aerated portions of lung receiving less blood: diffusion is not impaired and blood ventilation is not affected. In emphysema, the uneven gas distribution is associated with uneven but not balanced blood distribution; it can also be shown that blood ventilation is impaired even in areas receiving adequate air as a result of either some change in the alveolar membrane or an overall reduction in the pulmonary vascular bed. Bates considers that the carbon monoxide uptake test is a very sensitive indicator of emphysema and its progress. These studies will undoubtedly find wider clinical application in the future.

In discussing the clinical value of respiratory function tests, C. M. Fletcher stressed the difficulty of assessing quantitatively a subjective symptom such as dyspnœa. Nevertheless this must be attempted in order to distinguish the effect of anxiety in reducing exercise tolerance from the effect of actual ventilatory disability, and in order to assess progress and the capacity for work. In this he indicated the value of assessing ventilatory function during a standardized exercise test, especially when combined with some estimate of overall function such as the maximum breathing capacity.

Although assessment of respiratory function is not yet precise, a number of techniques for its investigation are coming within the realm of clinical practice. At this stage, further advances may be expected to provide a rational foundation for prognosis in emphysema, asthma and the pneumonokonioses, among other chronic lung diseases, and further research may well offer greater assistance to the thoracic surgeon in deciding on the value and scope of operative interference in a variety of conditions.

[1] M. J. AUSTRALIA, October 25, 1952.
[2] *Proc. Roy. Soc. Med.*, July, 1953.
[3] *Thorax*, March, 1953.
[4] *Thorax*, March, 1952.
[5] *Lancet*, July 4, 1953.

PLANT PROTEINS IN CHILD FEEDING.

IN the feeding of children cow's milk is of particular value as a supplement to the rest of the diet, particularly of high quality proteins. There are many parts of the the world where cow's milk is difficult to obtain or, if obtainable, is hygienically unsuited for the feeding of children and the development of other foods made from locally obtainable raw products and having the same general effect in the diet as cow's milk would have great practical value. During recent years much work has been done on combinations of plant products for this purpose. While a Medical Research Council team, under the direction of Professor R. A. McCance, was studying under-nutrition in Germany from 1946 to 1949, Dr. R. F. A. Dean, one of its members, was able to investigate the

value of mixtures of plant products as additions to the diets of school children and children living in orphanages. A report on the findings of these investigations has now been published by the Medical Research Council under the title "Plant Proteins in Child Feeding".[1]

Part I contains a discussion of the principles, a survey of past experience, and an account of some complicating factors in assessing the biological value of proteins. Here is a detailed study of protein and amino acid requirements of children in the first year of life and later. There is a good discussion on the assessment of protein values and the difficulties associated with the transfer of results of animal experiments to humans. Some proteins are damaged by heat; in other cases, particularly the soya bean, heating by destroying trypsin inhibitor improves the protein value. There is an excellent discussion on milk substitutes which have been used in the past. Soya bean has been the basis of many of these, and in some eastern countries this has been used extensively with varying success. It is shown that soya bean flour must be heated for a considerable time, preferably in an autoclave, to destroy trypsin inhibitor, to obtain the maximum food value. Failure to do this with the flour and other soya bean preparations has been responsible for many poor results. Commercial soya bean flour is a very variable product; some has all the fat retained, in some one-quarter to half of the fat is removed by mechanical pressure, and in some nearly all the fat is removed by solvent extraction. For the feeding of very young children, the most suitable preparation is probably a soya milk, made by spray-drying the liquid filtered from soaked, dehusked ground and autoclaved beans. It is expensive, however. A paste made from the whole autoclaved beans is also useful. In Malaya and Indonesia soya bean is rendered digestible by fermentation with a fungus, *Aspergillus oryzæ*. The use of this product for child feeding has not been studied to any great extent. Other seeds which have been used are almonds, coconut, sunflower, peanuts and rice. Malted wheat flour has been used for nearly two hundred years either alone or mixed with dried cow's milk or other animal sources of protein.

The future of milk substitutes made from plant materials would seem to depend on the use of a cheap, highly concentrated source of plant protein. The protein, too, must have a high biological value. At the moment the practical choice lies between soya beans and sunflower seeds, the latter in particular in those parts of the world where soya bean will not grow satisfactorily. There is considerable advantage in the mixing of plant proteins from several sources, for the amino acid deficiencies in one protein may be made up by excess of these amino acids in other plant proteins. Thus zein from maize is a highly deficient protein, but the mixture of zein with the other proteins of maize or other cereals makes a good source of amino acids. The addition of some animal protein, such as milk protein, to plant proteins greatly improves the value of the plant proteins.

The second part of the report deals with results obtained with children in Germany. The children were of all ages up to eleven years, including many between six months and two years old, an age group which is particularly difficult to feed well without milk. The diets contained little animal protein, and the general plan of the investigation was to give supplements of cow's milk or a cereal and soya mixture and to compare the effects on the children's growth and health. Four different mixtures of cereals and soya beans were used, and each of two of them was also used mixed with dried skimmed milk powder or with fresh skimmed milk. Type B, the one used most often, consisted of malted barley, wheat and soya flours, the soya flour being steamed for some time. This mixture contained 17·6% total protein. The other mixtures varied mainly in time of steaming of the soya flour. All the mixtures gave good results. Children of from one to two years of age who were given mixture B grew extremely well and were brought into good clinical condition, although they had no milk at all for sixteen weeks. When 25% of milk was added to this mixture greater progress was observed; anything less made no apparent difference. The more complete removal of trypsin inhibitor from mixtures C and D seemed to be beneficial, but manufacturing faults made this uncertain. When maize flour replaced wheat flour there was no apparent difference in the results. This was in type D, and this, used in the feeding of newborn children, gave good results so long as it supplied up to 4% or 50% of the total Calories, fresh cow's milk being used in addition. For children of from two to five years of age mixture B, and this with twelve and a half parts per 100 of skimmed milk powder, was little inferior to fresh cow's milk when 500 grammes of fresh milk or the caloric equivalent of the plant mixture was given. The malting of the barley flour was based on theoretical considerations and may not be necessary. It is not yet fully clear whether very young children can tolerate large amounts of starch.

It was perhaps inevitable that considerable stress should be laid, in this report, on the importance of soya bean. The soya bean stands preeminent among plants for its high fat, low carbohydrate, and very high protein content. In the amino acids of its protein the proportion of lysine is very high, making it especially suitable as a complementary food to cereals. It is probable that other sources of protein may be as good, and they need not be of plant origin. Vast quantities of skimmed milk are now wasted; and in some places fish might be considered as a good source of protein. This work is valuable, not only for the care of children in under-privileged parts of the world, but also as giving pointers for the feeding of children who find difficulty in using cow's milk.

[1] "Plant Proteins in Child Feeding", by R. F. A. Dean; Medical Research Council of the Privy Council, Special Report Series, Number 279; 1953. London: Her Majesty's Stationery Office. 9¾" × 6", pp. 171. Price: 10s. net.

PSITTACOSIS.

THE appearance of a paper in *The American Journal of the Medical Sciences* by W. W. G. Maclachlan, G. E. Crum, R. F. Kleinschmidt and P. F. Wehrle describing ten cases of psittacosis draws attention to this disease, which is certainly much more common than is usually supposed.[1] Psittacosis is a disease which is common in parrots in all countries and man is usually infected from these birds, but other birds such as pigeons, ducks and petrels may be infected and transmit the virus to man. The virus belongs to the psittacosis-*lymphogranuloma venereum* group, and there are some differences in the virus in different infections. In particular the virulence may vary from very little to very great. Infection has been found by Burnet in parrots from all States of Australia, mostly without apparent symptoms, but in 1938 severe outbreaks occurred in wild parrots in Victoria, South Australia and Tasmania with many deaths. Infected birds may be free from symptoms, but when they are kept in unhygienic conditions the virulence of the virus may increase, the birds become acutely ill, and human infections occur; but human infections have occurred from birds apparently healthy. There are considerable variations in the clinical picture in human cases from very mild influenza-like attacks to very severe atypical pneumonia. The onset in man is gradual or sudden with chills, fever, loss of appetite, sore throat, malaise and severe headache. There is very little cough and very little sputum, but the condition may progress to a severe pneumonia affecting several lobes of the lungs, sometimes with pleuritis and pericarditis. A lasting immunity usually follows an attack. Maclachlan *et alii* draw attention to the palpable enlargement of the spleen seen in most cases. The only certain criterion for diagnosis is the finding of antibodies to the virus in the blood, but an enlarged spleen in a case of atypical pneumonia with a low leucocyte count should make one think of psittacosis, particularly if there has been contact with parrots. Most of the fatal cases occur in the age group forty to sixty years. Inquiry among parrot fanciers in Sydney has brought to light a number of cases which were possibly mild psittacosis and a few severe cases of atyphical pneumonia mostly diagnosed as post-influenzal pneumonia.

[1] *Am. J. M. Sc.*, April, 1953.

Abstracts from Medical Literature.

PHYSIOLOGY.

Temperature and Blood Flow in the Forearm of the Eskimo.

G. M. BROWN, J. D. HATCHER AND J. PAGE (*J. Appl. Physiol.*, February, 1953) report an investigation of the forearm temperature and blood flow which has been carried out on the Eskimo in the Arctic and on Canadian medical students in a temperate climate. All observations were made at the low ambient temperature which the Eskimo requires for comfort. The degree of spontaneous fluctuation in forearm blood flow is greater in the Eskimo and increases in both groups as the local temperature of the forearm increases. In water baths with a temperature above 38° C. a more rapid increase in blood flow occurs in the Eskimo. The increased blood flow in the forearm of the Eskimo in extremely cold baths is unaltered by distant noxious stimuli. The volume of forearm blood flow is the same in both groups when maximum vasodilatation is produced by baths with a temperature of 45° C. The blood flow of the Eskimo in the clothed forearm and at any given waterbath temperature below 45° C. is greater than that of the white man. This is in agreement with the suggestion of increased heat production in the Eskimo. In water baths with a temperature below 38° C. the forearm muscle temperature of the Eskimo is less than that of the control group. It is probable that a greater cooling of arterial blood and, consequently, of muscle occurs as a result of the greater venous return in the Eskimo. The increased circulation in the hand is very important in this respect. A reversal of this arterio-venous heat exchange appears to take place at 45° C.

Adaptive Changes during Exposure to Cold.

L. D. CARLSON, H. L. BURNS, T. H. HOLMES AND P. P. WEBB (*J. Appl. Physiol.*, May, 1953) report work on a few subjects carefully studied under similar conditions. They state that skin and body temperature patterns on exposure to cold seem to confirm the hypothesis that an adapted person tends to keep extremities warmer and increase the "shell" participating in heat loss. This allows the adapted person to endure exposure to cold with less discomfort and loss in manipulatory efficiency and, if able to rewarm periodically, to call less on metabolism in response to cold. Existing data on men and animals confirm the hypothesis presented.

Assay of Resuscitation Procedures.

H. G. SWANN, M. BRUCER AND B. R. KING (*J. Appl. Physiol.*, February, 1953) report an assay of resuscitation procedure which they have designed. The method depends upon demonstrating the threshold of death for each procedure and then comparing the loci of the several thresholds in the process of death. The threshold of death is shown to be experimentally and sharply definable: it is the last point during the terminal decline of systolic blood pressure at which a given resuscitation procedure uniformly succeeds. Dogs breathing nitrogen were used for the tests. A positive and negative pressure respiratory pump was found to be eleven seconds superior to periodic oxygen insufflation, the margin of superiority residing in the fact that it uniformly succeeds in resuscitating at a point eleven seconds later in the process of death. Similarly, the suck-and-blow pump is three seconds superior to insufflation with 5% carbon dioxide in oxygen. The carbon dioxide at a 15% level is not superior to any of the above. Manual artificial respiration succeeded in only 19% of trials, the cause for its inadequacy being its failure to ventilate the lungs with even the minimum requirement of air. Attempted resuscitation of dogs by the Eve (tilt-board) method also fails in a large fraction of cases. The differences shown for the three methods involving insufflation are so small that for practical purposes all three may be considered equal in efficacy. In turn, insufflation of even minimal quantities of oxygen, as with a single oxygen insufflation or insufflation with 2% oxygen in nitrogen, is equal in efficacy to all other insufflation procedures. These data reinforce the conclusion that the critical need in resuscitation is oxygen and that the method of giving it is immaterial, provided that it gets into the lungs. The data also demonstrate that the amount of blood circulated by the positive and negative pressure respiratory pumps is too small to be of any practical importance in resuscitation.

Pulse Rate, Blood Pressure and Vision After a Cold Hip Bath.

A. H. STEINHAUS AND G. WENDHUT (*J. Appl. Physiol.*, May, 1953) report that a cold hip bath was administered a total of 43 times to a series of healthy male students in an experimental procedure designed to show the effects of this bath on pulse rate, blood pressure and circulatory adjustment in the change from a reclining to a standing position. Changes in these circulatory functions before and after the bath are compared with corresponding changes on 39 control days when no bath was taken. The following changes are attributed to the bath: (*a*) a slowing of the resting pulse rate with the subject in a reclining and in a standing position; (*b*) a reduction of the increase in pulse rate that normally occurs when a reclining person assumes the standing position; (*c*) an increase in the difference between the systolic pressure of the subject in reclining and standing positions, and also more cases in which the pressure rises on standing. All these changes were observed forty-five minutes after the bath. Some of them persisted for two hours. The authors state that all the observed circulatory changes shift somewhat the burden of maintaining blood pressure from the heart to other mechanisms. Two possible mechanisms are postulated. Under conditions of very low illumination the bath was shown to improve visual efficiency for at least one hour.

Factors Influencing Cholesterol Absorption.

K. S. KIM AND A. C. IVY (*Am. J. Physiol.*, November, 1952) have endeavoured to resolve some of the confusion surrounding the absorption of cholesterol. They report that fat in adequate quantities facilitated the absorption of cholesterol as determined by the difference between dietary and fæcal sterol levels. The fatty acid portion of the neutral fat molecule was found to be the active factor which facilitated cholesterol absorption. The glycerol portion was without effect. Serum cholesterol levels were significantly higher in the groups of animals receiving cholesterol and oleic acid than in those receiving cholesterol and corn oil. Cholic acid added to the diet significantly raised the serum cholesterol levels in rats receiving cholesterol and oleic acid. Cholic acid or desoxycholic acid added to the diet raised serum cholesterol levels only slightly in rats receiving cholesterol and corn oil, but the increase was not statistically significant. Addition of extra desoxycholic acid to the diet containing corn oil did not increase cholesterol absorption. Excretion of phospholipid in the fæces varied with the diet. When a fat-free diet was given, only a trace of phospholipid was found in the fæces, and the addition of cholesterol or glycerol to a fat-free diet did not alter the phospholipid excretion. But when corn oil was fed there appeared appreciable amounts of phospholipid in the fæces, and this was further increased by giving various free fatty acids. Oleic acid was more potent than palmitic acid in stimulating phospholipid excretion. The addition to the diet of free fatty acids derived from corn oil increased the fæcal phospholipid excretion approximately 14 times above the level found when an equivalent amount of corn oil was given. From this finding it was estimated that 7% of the corn oil fatty acids was split off in the intestine prior to absorption. Thiouracil increased the serum cholesterol content significantly even when the diet contained neither fat nor cholesterol. Cholesterol did not prevent the body weight loss induced by the giving of thyroid powder, but corn oil was found to diminish the body weight loss considerably. A considerable sex difference was noted in response to thyroid powder. Desoxycholic acid was found to be much more toxic to male than to female rats. Male rats could be protected by the following dietary additions in the order of their effectiveness: cholesterol, corn oil, and cholesterol *plus* corn oil.

Studies on Hypothermia.

F. GOLLAN, P. BLOS AND H. SCHUMAN (*Am. J. Physiol.*, November, 1952) report that a pump-oxygenator based on the principle of gas dispersion was used to produce rapid changes in body temperature in 33 dogs. The rate of cooling achieved was twice as fast as that obtained by immersion. Blood pressure, respiratory rate, heart rate and electrocardiographic tracings resembled closely the changes found in immersion hypothermia. During cooling, available blood flow in the venous catheters showed a great reduction which could not be influenced by the intravenous administration of fluid. Rewarming restored blood flow to pre-cooling levels. By shunting oxygenated blood equivalent to the cardiac output from the right side of the heart into the aorta, acute cardiac crisis was avoided during the perfusion. All animals cooled to 29° C. survived, there was a rising mortality from 29° to

27° C., and all animals below 27° C. died of ventricular fibrillation as a complication of cardiac catheterization.

Measurement of Renal Blood Flow.

H. L. CONN, JUNIOR, W. ANDERSON AND S. ARENA (*J. Appl. Physiol.*, May, 1953) report on a gas diffusion method with nitrous oxide which has been proposed as a method for the measurement of renal blood flow, particularly for clinical application to the anuric patient. They describe the general theory of such a method and a technique for its application to the renal circulation. This method was compared under varying experimental circumstances with a standard reference of flow, the bubble flow meter, and a close correlation was obtained. The mean difference was –0·01, the standard deviation was 0·068 and the *t* value was 0·6 for 17 clearance periods.

BIOCHEMISTRY.

X Irradiation.

J. S. ROTH *et alii* (*Arch. Biochem.*, May, 1953) subjected rats to 600*r* of total body X irradiation and studied changes in enzyme activities and oxygen uptake for a twelve-day period. Changes were observed in liver catalase, xanthine oxidase, ribonuclease and serum lipase. No significant alterations were observed in oxygen uptake of liver and kidney, or in choline oxidase, lipase and cathepsin activity of liver.

Fluoride.

H. G. MCCANN (*J. Biol. Chem.*, March, 1953) has investigated the reactions between fluoride ion and hydroxyapatite over a range of fluoride of one part per million to 9·5%, and over a calcium to phosphorus ratio in the apatites of 1·593 to 1·665, with results indicating that the type of reaction is chiefly dependent on these two variables. Fluorapatite is formed at all ratios of calcium to phosphorus at a few parts per million of fluoride, calcium fluoride or fluorapatite is formed up to 0·2% of fluoride, depending upon the calcium-phosphorus ratio, and calcium fluoride is formed at all ratios at high fluoride concentrations.

Diethylstilbœstrol.

J. REILLY (*Arch. Biochem.*, March, 1953) has demonstrated that diethylstilbœstrol inhibited the endogenous respiration of cat heart tissue slices. Added substrate did not influence the inhibitory effect of diethylstilbœstrol on slice respiration. When cat heart homogenates were used, the diethylstilbœstrol inhibited the enzymes oxidizing succinate, fumarate, malate and oxalacetate.

Amino Acids.

W. H. STEIN (*J. Biol. Chem.*, March, 1953) has used chromatography on Dowex 50 columns to determine the ninhydrin-positive components of the urine of young adult males. Quantitative values for the following have been obtained: taurine, threonine, serine, asparagine, glycine, alanine, amino adipic acid, cystine, valine, isoleucine, leucine, tyrosine, phenylalanine, histidine, methyl histidine and lysine. The virtual absence (less than 10 to 15 milligrammes per day) of aspartic acid, proline, methionine, citrulline, glucosamine, hydroxylysine, ornithine and arginine has been established. Glutamic acid appears also to be absent from freshly passed urine, but arises as the urine stands for a period of days. Of the approximately one gramme per day of amino acids determined, about 70% may be accounted for as the four amino acids taurine, glycine, histidine and methylhistidine. There are a number of peaks on the urine curves, the full interpretation of which requires further study. Chromatography of acid hydrolysates of urine reveals that the quantity of almost every amino acid is increased. The data indicate that about two gramms of amino acids are excreted per day in the conjugated form. Glycine and glutamic and aspartic acids comprise the major part of the conjugated amino acids.

Lactose.

E. DIMANT *et alii* (*J. Biol. Chem.*, March, 1953) have shown that lactose synthesized in a bovine mammary gland perfused with blood containing 1-C^{14} glucose contained nearly equal amounts of radioactivity in the glucose and galactose moieties. The C^{14} was located almost exclusively in carbon atom 1 of each of the monosaccharides. The data are consistent with the possibility that similar enzymatic pathways are involved in converting glucose to galactose in the mammary gland and ingested galactose to glucose in the non-lactating animal.

Progesterone.

J. G. WISWELL AND L. T. SAMUELS (*J. Biol. Chem.*, March, 1953) have shown that the *a*, *β*-unsaturated ketone structure in ring A of progesterone disappears on incubation with liver tissue *in vitro*. The process is accelerated by citric, isocitric and cis aconitic acids and by other metal-binding agents. It appears, therefore, to be inhibited by metal ions. The reaction seems to be a reduction of ring A, since it proceeds at normal rates under very low oxygen tensions.

Cholesterogenesis.

G. M. TOMKINS *et alii* (*J. Biol. Chem.*, March, 1953) have studied the influence of cholesterol feeding upon hepatic cholesterogenesis. When a diet containing 5% cholesterol was given for eight days, cholesterol synthesis from acetate in the liver practically stopped. A pronounced depression in synthesis was observed in livers of rats fed 0·5% cholesterol in a diet for seven days. An effect upon synthesis was also noted after a single feeding of cholesterol. The view is proposed that cholesterol synthesis in the liver is under homœostatic regulation by dietary cholesterol.

Tyrosine Metabolism.

M. C. C. WU *et alii* (*Arch. Biochem.*, June, 1953) have reported that vitamin B_{12} decreased the excretion of tyrosine metabolites by guinea-pigs on an ascorbic acid-deficient diet. The nature of the action with dosage at the microgramme level was similar to liver extract effect, either with single or with repeated injections. The relation of vitamin B_{12} to ascorbic acid was studied in relation to ascorbic acid saturation. The authors state that the 20 milligramme dose of vitamin B_{12} was found to lose its effect in prolonged scurvy, which indicates the requirement of ascorbic acid for the vitamin B_{12} effect. No clear correlation can be evaluated between tissue ascorbic acid and vitamin B_{12} effect; liver ascorbic acid may play a more important part in the vitamin B_{12} effect. The ascorbic acid depletion method was applied to a study of the folic acid effect in tyrosine metabolism. It was concluded that not only is a given level of folic acid necessary to produce an effect on tyrosine metabolism, but, also, with a given effective dose of folic acid, a minimum ascorbic acid saturation must be achieved.

Vitamin A.

A. ROSENBERG AND A. SOBEL (*Arch. Biochem.*, June, 1953) have shown that conversion of carotene to vitamin *A* in the isolated small intestine of alloxan-diabetic rats is greatly diminished as compared with the effect in non-diabetic littermates. The authors state that this finding helps explain the low liver vitamin *A* stores of alloxan-diabetic rats fed carotene and further indicates that the intestine is a major carotene conversion site.

Pyridoxine.

E. F. CALDWELL AND E. MCHENRY (*Arch. Biochem.*, July, 1953) have investigated the activity of aspartic-glutamic and alanine-glutamic transaminases in rat liver with different amounts of casein in the diet, and in the presence and absence of dietary pyridoxine. Activities of these enzymes varied with the protein content of the diet, and were elevated when caloric intake was restricted, provided that dietary pyridoxine was available. The relative effect of omission of pyridoxine from the diet increased greatly when the amount of casein was raised or lowered from 20%. The alanine-glutamic reaction appeared to be the more sensitive of the two to the dietary omission of pyridoxine. A sex difference was frequently observed in both transaminases, the male level being higher. In pyridoxine-deficient rats, a decrease in aspartic-glutamic transaminase activity in the liver appeared to be coincident with an elevated rate of urea formation.

Collagen.

W. VAN B. ROBERTSON AND B. SCHWARTZ (*J. Biol. Chem.*, April, 1953) have described a method for inducing, within a short period, the development of a tissue containing relatively large amounts of collagen. Ascorbic acid was needed for collagen formation in this tissue. The rapid formation of a large collagen-containing tissue increased the nutritional ascorbic acid requirement of guinea-pigs.

Acid Phosphatase.

K. TSUBOI AND P. HUDSON (*Arch. Biochem.*, April, 1953) have investigated the phosphomonoesterase action of human erythrocytes using as substrates phenyl phosphate, *α*-glycerophosphate and *β*-glycerophosphate and yeast adenylic acid. Only one pH optimum of enzyme action, about 5·5, was observed with each of the substrates tested. The enzyme was activated by magnesium in the presence of all the substrates investigated.

Special Articles for the Clinician.

(CONTRIBUTED BY REQUEST.)

LXXXIX.

TREATMENT OF ALCOHOLISM.

An individual may be said to need treatment for alcoholism if the continuance of the alcoholic habit constitutes a threat to his mental or physical well-being or to his social security.

In attempting to treat cases of alcoholism, it is all-important to recognize one basic fact—namely, that alcoholism is a symptom of an underlying psychological disorder. The main problem is to discover this underlying cause, and to treat it, rather than to attempt to treat the alcoholism *per se*.

It is of importance, when confronted with an alcoholic patient, to determine whether he can be satisfactorily treated by medical methods, and if so, what degree of improvement can be expected. The fact that an alcoholic has been brought to a doctor (often against his will) is not necessarily an indication that responsibility for management should be undertaken. A patient will not participate fully in treatment unless he has a real "need" within himself for assistance. That a relative declares that the patient needs treatment is not in itself an indication that the patient himself feels this need. This will be referred to later.

The first step in management is a careful determination of the following: (*a*) The physical state. (*b*) The psychological state. (*c*) The patient's "need" in treatment. (*d*) The form of treatment.

Assessment of the Physical State.

Physical examination may reveal causes or effects of alcoholism. Causative physical conditions include those which reduce tolerance for alcohol and interfere with cerebration, judgement or other personality functions which promote stable existence. Again illness may, by its effects, produce a psychological problem from which the patient finds escape by taking alcohol in excess. Diseases of particular importance in respect of the above include cerebral arteriosclerosis, hypertensive encephalopathy, cerebral syphilis, brain tumour, senility, post-traumatic cerebral disturbance, sequelæ of cerebro-spinal infections, chronic renal diseases and chronic anæmias. Any illness which is associated with severe pain or disabling deformity or disfigurement can play a part in provoking a need for alcohol as an escape. The most common pathological conditions resulting from alcoholism are malnutrition, hepatic cirrhosis and polyneuritis. In general, treatment of alcoholism in an individual who is physically ill is more likely to be successful if some substantial improvement of the physical state is possible. The presence of physical disease, the effects of which persistently interfere with cerebration, reduces the possibility of lessening the severity of its attendant symptom of alcoholism.

Assessment of the Psychological State.

Assessment of the psychological state provides information on the patient's intelligence, emotional state and general character structure. It may be important to have a psychometric determination of the intelligence carried out by a psychologist. This will reveal the presence of congenital mental defectiveness or of acquired mental deterioration due to associated physical disease or to the chronic alcoholism itself. Should the mental defect from any cause be of severe degree, treatment is not likely to be successful. Assessment of the emotional state of the patient will indicate whether alcoholism is in this instance a symptom of neurosis, and if so, whether the emotional reaction is due to external environmental causes or whether it represents an expression of deep-seated unconscious emotional conflict. An appraisal of these factors will indicate whether on the one hand it is possible to alter the environment in order to reduce stresses, or whether on the other hand the type of mental conflict is likely to respond to psychotherapy or to those forms of physical treatment available to the psychiatrist. Such an assessment will, of course, determine suitability for treatment as well as prognosis. In general terms, those individuals with psychoneuroses due mainly to external environmental pressures will do better with treatment than those whose deep-seated dependency or aggression stems from causes not readily accessible to psychotherapy. In individuals whose alcoholism is a symptom of recurrent depression, the successful treatment of the depressive attack with electroshock would make the outlook favourable.

Personality assessment is, of course, part of the psychiatric examination of the emotional status, but special mention must be made of constitutional personality defect or psychopathy. The psychopath will show evidence of instability from very early childhood. In particular, he will have an unstable occupational record and will prove himself inconsistent, unpersisting and unreliable in all spheres of human relationships. His uncontrolled aggressiveness or his social or emotional inadequacy may manifest itself in alcoholism, and treatment by any measures other than legalized restriction is not likely to succeed.

The Patient's "Need" for Treatment.

In view of the opinion expressed that alcoholism is not in itself a disease, the simple unqualified statement from a patient that he wishes to be cured of alcoholism is not a sound basis of approach. It is necessary to be sure that the "need" comes from within the individual and is a real one, not merely resulting from the threats or persuasions of relatives or friends, or from some optimistic and irresponsible urge of the moment masquerading as a "good resolution". Psychiatric interview will help in uncovering the patient's real "needs" for treatment; and if these can be well defined, progress is hopeful. The usual needs are for conditions of dependency, release of tension, solution of environmental problems or release from other distressing emotional conflicts. In such cases it is important to concentrate all attention upon these and not upon the habit of alcoholism.

Assessment of the Appropriate Form of Treatment.

Assessment of the appropriate form of treatment may include one or more of the following: attention to physical health, environmental manipulation, psychotherapy, treatment with drugs, social therapy, "Alcoholics Anonymous", legalized restriction. The choice of treatment depends on the assessment previously outlined. It can be said that the cornerstone of all treatment of alcoholics is in a relationship formed by the therapist with the patient. This relationship is influenced substantially by the emotional attitude of the therapist towards his patient. Already, by his exasperated relatives or friends, he has probably been treated with one or other of the following: over-concern, rejection, persuasion, exhortation, punishment, direction, threats, pleadings, contempt, disgust, open aggression or a combination of these. Most of these methods are of temporary value at the best.

I believe that the attitude of the physician should approximate to that expressed in the following "statement" to the patient. This is, of course, not actually stated to the patient in so many words, but it is clearly implied by the attitude adopted by the physician towards the patient:

"I like you, and will continue to do so, and I will not become angry or aggressive with you although I know it is almost certain that you will become so with me. You have an illness and this illness is not primarily due to your drinking to excess. It is true that you have an insatiable thirst, but that thirst is really an unsatisfied thirst for emotional security, affection and a sense of self-esteem which you have never really enjoyed since you were a child. It is in this respect that you are ill and need treatment, and not primarily because you are an alcoholic.

"I will not stand in judgement upon your behaviour as an alcoholic, because on the one hand pronouncements upon ethics and morality are not my professional business, and on the other, you would take as little notice of such pronouncements as you have taken of similar strictures delivered by your relatives and well-meaning friends. I will not use my medical authority to threaten you with the prospect of early death through alcoholism, because you will readily recognize this as a disguised moral stricture, and in any case you may prove me wrong for a considerable period of time. I will invoke the law only as a last resort, to terminate your social destructiveness and the misery you inflict upon your environment. If I do so, it will represent a gesture of medical failure. I will not threaten you with this course, because I know that either you may be unable to look beyond the immediate moment of oral gratification, or you are deliberately seeking oblivion or near death to save you from your own conflicts, and therefore you are not easily made afraid. It may be, too, that you are much more afraid by reason of your own sense of guilt than I can make you.

"I promise not to exhort you or direct you on the straight and narrow path, because already your friends have attempted this with greater vehemence, enthusiasm and persistence than I can muster. If there is any power through exhortation toward sobriety and stability, it is vested in your spiritual advisers and what remains of your own conscience. It is quite possible that if you do believe in a Power greater than that possessed by man, you will be assisted by availing yourself of it.

"You must not expect me to be moved to an optimistic credulity either in your own sudden resolves to rehabilitate yourself, or in your expressed confidence in my ability to assist you by a few magical manœuvres. Nor will I be moved by your despondency at your almost certain failures to remain sober during the course of your treatment. That is to say, your so-called successes or failures will arouse no emotional response in me.

"These are the things I will not do; there are, however, things I will do for you, but these will be with your participation. I will help you to understand yourself and why it is that you prefer immature and immediate satisfactions to mature ones. I will try to teach you to achieve mature emotional satisfaction in relationships with other people by discussing with you the techniques by which this can be done. This may allow you to extract from such relationships affection, self-esteem and a sense of belonging to them and being important to them. You may learn how these relationships will bring you such peace of mind that their continuance will strike you as being worthwhile. You may learn, too, in your relationship with me, that immature discharge of aggression leads to little emotional reaction in me and neither hurts nor irritates me, and you may in the end achieve avenues of mature aggressive discharge that affords some permanent relief of the tensions within you.

"You will find that the essence of your treatment will consist in the development of a relationship with me which will initially be one of dependence upon me. In return for this dependence I will offer you approval, affection and the knowledge that you may rely upon me at all times. This may help to compensate for the lack of approval and emotional warmth which you experienced as a child.

"During your treatment little attention will be given to your alcoholism, but a great deal to an examination of your life situation and your personality make-up. You will be assisted to examine all internal and external stresses which lead you into tension and conflict, and to find socially acceptable and constructive means of defending yourself against the pain which these tensions induce.

"I have said that I will not threaten you, but this is not quite correct. You will find that the price of continuing dependence upon me and of my approval of you will be an increasing state of maturity in yourself. Should you continue to behave in an immature way or try to achieve immature satisfactions in your relationship with me, just as you have with other people, then you will find in me, not anger, not abuse, but disinterest and detachment, and you may not like this. It will not matter to me whether your immaturity expresses itself in the taking of alcohol in excess, or whether it is in the more important general field of interpersonal relationships. In either case it will be met with a lessening of a sense of security in your relationship with me.

"If you fail, then it will be my failure as well as yours."

It will be seen, then, that the psychological treatment of alcoholism implied by the foregoing aims at making the patient dependent on the therapist, who seeks to use this dependency to orientate the patient to forms of thinking, feeling and acting more mature than those to which he has been accustomed. Throughout treatment, which must be regular and prolonged, the therapist aims at maintaining a friendly, approving and permissive attitude to the patient, and he persists in this attitude for as long a period as the patient gives indications of making some contribution to the relationship. It will be seen that in this treatment there is no place for exhortation, preaching, implied or actual punishment, or directiveness.

In some instances it will be found useful to employ deeper forms of psychotherapy, and in carefully selected cases there is a useful place for more thorough abreactive techniques and for psychoanalysis. Some workers have claimed success with hypnosis.

In addition to relationship therapy, as outlined above, or to the other psychotherapeutic techniques mentioned, efforts should be made to make such alterations in the patient's external environment as are practicable. The resolution of interpersonal tensions causing or resulting from alcoholism may call for great skill and tact. Modification of the attitude of the family of the alcoholic, where such is possible, may be of great value. In the field of external stresses, some assistance may be given by improving external living and working conditions in such a way that the patient's new incentives are not crushed by social or economic pressures.

The application of socially directed therapies is of some value. In its simplest sense this may mean enlisting the interest of other groups of individuals who will make the alcoholic feel more secure and "wanted" by his fellows. To enlist the assistance of church institutions and of social and cultural clubs may be of great value in providing the alcoholic with the supportive momentum of a group of well-orientated fellow individuals.

A more specific form of group assistance is to be obtained from group psychotherapy conducted by a psychiatrist in a clinic. In general, such groups are small collections of patients who through mutual discussion and ventilation of their problems come to achieve a more mature approach to them by understanding the problems and needs of other patients in a similar type of mental conflict.

"Alcoholics Anonymous."

"Alcoholics Anonymous" is a world-wide cooperative organization of former alcoholics who have formed themselves together in small groups of individuals whose only purpose is to help the sick alcoholic to recover, if he so wishes. The society has no complex organization within its membership and cooperates with both the medical profession and the Church in dealing with the problem of the alcoholic. The only essential requirement for membership is a desire to recover from the illness of alcoholism. Although there is a spiritual approach to the problem, this is not obligatory, and "Alcoholics Anonymous" members stress the spiritual aspect only because they have found during the course of recovery that they cannot do without some kind of belief in a power greater than that of man. There are twelve so-called "steps" in the process of recovery. The patient must be convinced that he cannot manage his own problems and that he will achieve success only by accepting help from others. He learns to analyse his own make-up both personally and sometimes during mutual discussion. In such discussion it is likely that he will release much tension in relation to his own problems and so obtain relief. The member is confronted with both the opportunity and the necessity to improve relationships with his fellows. Finally, he obtains added strength by working with other alcoholics who are in an earlier phase of recovery. Adherence to the above principles is, however, not a condition of "Alcoholics Anonymous" membership.

It has been found that one alcoholic can talk to another with a sense of understanding and proximity which is not always possible when the alcoholic is in the presence of his doctor or his spiritual adviser; he feels that he is understood and that he will not be preached at or judged. He also finds that the rationalizations and excuses usually offered to and sometimes effective with a doctor or a clergyman will not be convincing when offered to a fellow alcoholic.

"Alcoholics Anonymous" usually hold group meetings weekly, when experiences are related, and problems discussed. All members are urged to read their book "Alcoholics Anonymous". Members work with new alcoholics, who are making their initial contact with the group. "Alcoholics Anonymous" groups exist throughout Australia, and there are facilities for keeping members in touch who may be geographically separated from other members of the group.

In general it can be said that "Alcoholics Anonymous" has a great deal to offer the alcoholic who feels that his problem has gone beyond his control and who wishes to recover from his illness.

"Antabuse."

"Antabuse" (diethyl-thiuram disulphide) is an apparently non-toxic substance producing no significant symptoms if taken alone in the usual dosage. If, however, alcohol is taken in addition, characteristic symptoms occur within ten minutes, becoming maximal in about thirty minutes. The symptoms include a sensation of heat in the face, flushing, dilatation of scleral vessels, palpitation, dyspnœa followed by nausea, vomiting and pallor. Headache and insomnia occur. The symptoms are apparently due to an increase in the formation of circulating acetaldehyde, the blood acetaldehyde level rising to as much as five times that of the normal level in individuals who have taken the same dosage of alcohol but without "Antabuse". There are dangers of

right-sided cardiac failure following even small quantities of alcohol taken in conjunction with "Antabuse". Some deaths have been reported. The reason for this is not quite clear, but the lesson to be learned from it is the advisability of giving a small preliminary test dose of "Antabuse" and alcohol before commencing routine treatment.

Treatment should be initiated in hospital in order that any untoward reaction may be noted and dealt with. The drug should never be given without the patient's knowledge and cooperation, and it is wise to avoid any suggestion that the treatment or attendant reactions are in the nature of physical punishment for the taking of alcohol. It is important that the nursing staff should not express to the patient any of the slightly sadistic glee that they may occasionally feel when the patient has had what they smilingly refer to as a "good reaction". Should the patient during treatment adopt the attitude that the therapy is in the nature of a trial of strength between himself and the effects of the drug and should he attempt to "drink past" the unpleasant symptoms, in order, as it were, to prove the efficacy of the proverbial "hair of the dog", then treatment should be discontinued at once, as persistence with it in these circumstances may become dangerous.

Dosage.

Various regimes are advised. The following has been found useful. The patient should be free of alcohol for forty-eight hours prior to the commencement of treatment.

Half a gramme of "Antabuse" is given thrice daily for three days. On the third day of such dosage a test dose of one drachm of brandy or whisky is given in order to determine whether there is any excessive reaction to small doses. If such reaction does not occur, on the fourth day "Antabuse" half a gramme is given twice a day, and at 11 a.m. alcohol is administered. It is usual to give the form of alcohol the patient usually consumes. For example, he may be given a glass of beer or the usual-sized glass of whisky, brandy, gin or sherry. If there is no preference, hospital brandy is quite satisfactory. If there is no marked reaction, a second dose is given thirty minutes after the first. This is usually followed by rise in pulse rate, flushing, headache, nausea or sleepiness. It is worth while to continue the dosage until such symptoms do occur, and upon one occasion, at least, to induce vomiting. If an adequate reaction is not produced with three doses of alcohol at half-hourly intervals, it is an indication to raise the dosage of "Antabuse" by 0·25 or 0·5 gramme. Should a satisfactory reaction occur with the taking of two doses of alcohol, the taking of a third is left to the discretion of the patient, who usually declines. On the fifth and sixth days "Antabuse" is given twice daily, and the patient's reactions are tested to alcohol at 3 p.m. on the fifth day and at 9 p.m. on the sixth day. On the seventh day, "Antabuse" dosage is reduced to half a gramme given in the morning, and on the seventh and eighth days the patient is tested in the morning and in the evening. The remaining two days are used in order to stabilize the patient on the existing dosage or to make trial increase or decrease in dosage, depending on the quality of the reactions previously obtained. It will be seen then that the general aim of treatment is to produce a satisfactory reaction with the smallest dose of "Antabuse" practicable, the dose to be given in a single morning administration, and to produce a reaction with one or two doses of alcohol.

On discharge from hospital the patient is requested to report in one month, then once every month for at least eighteen months. During this time he continues to take "Antabuse" in the dosage originally determined. Some sort of psychotherapeutic contact with the patient is essential for at least one year. This contact should be at least once in every month. In fact, if psychological and social therapy is not undertaken in association with the "Antabuse" treatment, it is of very little value, since in such cases it is likely that the patient will adopt the attitude that the treatment is a method of punishment for his alcoholism, and he will in consequence feel unsupported and rejected and will either discard the treatment himself or contrive convenient "holidays" from "Antabuse", in order to allow himself to proceed on planned sprees.

Delirium Tremens.

With *delirium tremens* it is very seldom necessary to withdraw alcohol gradually, and little harm results from abrupt withdrawal. The immediate treatment following withdrawal is directed towards sedation, feeding, general nursing and avoidance of infection. It is as well to avoid barbiturate medication if possible, although initially intravenous administration of "Sodium Amytal" or "Pentothal" may in very acute cases allow the physician to gain control of an otherwise uncontrollable patient. This control having been gained, a Rehfuss tube may be inserted through the nose to the stomach and drip-feeding commenced, attention to general nursing hygiene instituted, and appropriate restriction of the limbs arranged, if necessary. Following this initial narcosis, paraldehyde sedation by mouth or by tube appears to be the most effective and safest. Nicotinic acid in doses of 200 to 400 milligrammes daily is given together with riboflavine six milligrammes daily and 100 milligrammes of ascorbic acid. Thiamine is given intramuscularly or intravenously in doses of 50 to 100 milligrammes daily. The diet is fluid and high in protein content. The intravenous administration of 10% glucose-saline solution together with small doses of insulin has been recommended. Antibiotics

TABLE I.
Summary of Dosage of "Antabuse".

Days.	Amount of "Antabuse". (Grammes.)	Amount of Test Alcohol. (Ounces.)	Time.
1	0·5 thrice daily.	—	
2	0·5 thrice daily.	—	
3	0·5 thrice daily.	0·125 (1 drachm)	
4	0·5 twice daily.	2·0	11.0 a.m.
		2·0	? 11.30 a.m.
		2·0	?? 12.0 noon
5	0·5 twice daily.	2·0	3.0 p.m.
		2·0	? 3.30 p.m.
		2·0	?? 4.0 p.m.
6	0·5 twice daily.	2·0	9.0 p.m.
		2·0	? 9.30 p.m.
		2·0	?? 10.0 p.m.
7	0·5 at 9 a.m.	2·0	11.0 a.m.
		2·0	? 11.30 a.m.
		2·0	?? 12.0 noon
8	0·5 at 9 a.m.	2·0	9.0 p.m.
		2·0	? 9.30 p.m.
		2·0	?? 10.0 p.m.
9	±0·5 at 9 a.m.	2·0	11.0 a.m.
		2·0	? 11.30 a.m.
		2·0	?? 12.0 noon
10	±0·5 at 9 a.m.	2·0	9.0 p.m.
		2·0	? 9.30 p.m.
			?? 10.0 p.m.

are employed if there is any likelihood of supervening infection in the lungs. After the acute stage of *delirium tremens*, it is sometimes necessary to build up the patient's physical state with subcoma insulin therapy; this may be followed by a course of physical reeducation arranged through a physiotherapist or gymnasium. If the patient desires "Antabuse" treatment, this may be instituted after the acute phase of delirium has passed.

Chronic Alcoholism with Dementia.

When the stage of chronic alcoholism with dementia has been reached, it is often found necessary to commit the patient to an institution either by certification as insane or as an inebriate. If the degree of dementia is at all substantial, "Antabuse" treatment is of little value and indeed may be dangerous, since the patient may continue to take alcohol whilst still taking "Antabuse", disregarding the unpleasant attendant symptoms, with resultant circulatory failure.

In some instances, improvement may be obtained if it can be contrived to keep the patient under treatment in hospital for a minimum period of three months, preferably six. Feeding, sedation and massive vitamin therapy associated with occupational therapy and physical reeducation may be of value. It must be emphasized, however, that good progress so obtained may be quickly reversed when the patient leaves hospital and goes on further alcoholic bouts. In an attempt to avoid this, contact must be maintained with the patient each week or so in the early stages, and at least once monthly if possible for a year or two. In fact it is seldom safe to discharge an alcoholic as "cured".

Dipsomania.

Dipsomania is a state of alcoholic intoxication occurring periodically. It may be symptomatic of an obsessive-compulsive state or manic-depressive psychosis. The immediate treatment is that of acute alcoholism. It is sometimes possible to prevent or defer further attacks if the patient is interviewing a psychiatrist at regular intervals

and is receiving psychotherapeutic assistance. "Antabuse" is of value in some instances, though the patient is likely to discontinue "Antabuse" at the commencement of his compulsively predetermined attacks of drinking.

Alcoholism with Neurological Disorder.

Alcoholism with neurological disorder includes alcoholic polyneuritis. If dementia is also present, as in Korsakov's psychosis, treatment is directed towards the dementia, the addiction and the general physical state, which is commonly unsatisfactory. Neuritis is treated with massive doses of thiamine chloride 50 to 100 milligrammes daily, given intravenously or intramuscularly, and nicotinic acid 200 to 400 milligrammes daily. Passive movement and active exercises are of value when the initial stage of muscle tenderness has subsided.

Legal Restriction of Alcoholics.

Certification of a patient with acute alcoholism may occasionally be necessary if he is violent, destructive, aggressive or noisy. In uncomplicated cases, however, this measure is seldom worth while, since it is likely he will be discharged from a receiving ward as soon as he is sober, and as a result is usually resentful both of his relatives and of his medical attendant. Patients with dipsomania, *delirium tremens* or alcoholism with severe dementia may be transferred to the receiving ward of a mental hospital and retained during the psychotic phase.

Except for patients suffering from chronic alcoholism with severe dementia, the period of stay in a mental hospital is seldom long enough to influence anything but the immediate attack. It is possible, however, to commit a patient to a mental hospital, retreat or private psychiatric hospital under the terms of the *Inebriates Act*. Procedure varies in different States. In Victoria, New South Wales and Queensland facilities are available to implement the Act. South Australia has no such facilities at present. In general terms, a written application for committal is made through a solicitor to a magistrate, or in Queensland to a Supreme Court judge. The application may be made by the patient when sober, or by the husband, wife, parent, brother, sister, son or daughter, if of age, or the business partner of the inebriate. Affidavits are prepared by the applicant and one or two other persons who are in a position to give material evidence of inebriacy. One medical certificate in the form similar to that required for a certificate of insanity is completed by a medical practitioner, who must state facts observed by himself separately from facts communicated to him by others. The medical practitioner must, therefore, have seen the inebriate on more than one occasion in order to form his opinion. Hearing of the application is in private, and the inebriate may have legal representation if he desires. After this, a judge or magistrate may make an order for a period not exceeding twelve months, but this period may be extended from time to time.

Few patients are committed in this manner, and the conditions of this Act make it unsatisfactory in practice; in addition relatives of an inebriate are often very loath to make application. There are some advantages in committal to a private institution or to a retreat (Queensland). Since there are no institutions in Australia gazetted as institutions for inebriacy, it is necessary for a patient entering a State institution to be placed with patients certified as apparently insane or insane.

ALEX SINCLAIR,
Melbourne.

Medical Societies.

THE MEDICAL SCIENCES CLUB OF SOUTH AUSTRALIA.

A MEETING of the Medical Sciences Club of South Australia was held in the Anatomy Theatre, New Medical School, Frome Road, Adelaide, on September 4, 1953.

The Physiology and Pharmacology of Blood Vessels.

DR. F. LIPPAY read a paper entitled "Some Problems Concerning the Physiology and Pharmacology of Blood Vessels".

Trace Elements and Microorganisms.

DR. R. J. SWABY, in a paper on trace elements and microorganisms, said that very little was known about the trace element requirements of microorganisms because those requirements were minute and present methods for purifying media were suitable only for simple synthetic media. Recrystallizing salts and sugars was rarely sufficient, so chelating agents or adsorbents had to be used to remove trace elements. When that was done, a number of soil microorganisms were found to have similar requirements to those of green plants. Consequently microorganisms, particularly fungi such as *Aspergillus niger* and *Curvularia*, might be used instead of plants for rapidly bioassaying the amounts of micronutrient elements available from soils. Microbial bioassay was well correlated with plant response for copper and molybdenum, less so for zinc; but it was almost useless for manganese and iron, where microorganisms obtained manganese and iron (probably from crystalline oxides) not available to plants. In a survey of over 400 soil samples from eastern Australia with *Aspergillus niger* the commonest deficiency was zinc, then copper, followed by molybdenum, while very few soils were deficient in manganese and iron. In addition, a number of soils were found which actively fixed added trace elements so that the fungus had difficulty in releasing them. That was particularly true in calcareous soils, where calcium carbonate was responsible for firmly adsorbing iron, zinc and copper. Microbial bioassay provided an accurate method for determining the amounts of iron, zinc, copper, manganese and molybdenum in plant ash without the necessity of removing interfering elements, so troublesome in chemical estimations.

Transplantation of Skin in the Fœtal Lamb.

MR. P. G. SCHINCKEL, in a paper on transplantation of skin in the fœtal lamb, said that the literature suggested that the fœtus was unable to make an immune response. Most experimental work in the past had been carried out on chickens with bacterial and viral antigens. The ability of fœtal lambs to make immune responses had been examined by means of skin homografts. Skin autografts and homografts had been performed in 16 fœtal lambs between the ages of 80 and 117 days. By means of histological examination following grafting, and visual and histological examinations after birth, and by the use of second-set homografts, it was shown that homografts were actively rejected by the fœtus. That rejection gave every indication of belonging to the general class of actively acquired immune responses and confirmed at the fœtal stage the observations of Medewar on young and adult animals. Homografts in which the ewe was used as donor were also rejected by the fœtus, indicating that the reaction was of fœtal and not maternal origin.

Two possibilities were suggested to account for the discrepancy between these observations and those made with chickens. Firstly, it was possible that the fœtal lamb acquired an immune response mechanism at a much earlier age than did the chicken. Secondly, it was possible that the fœtus was unable to respond immunologically to antigens which had a determinant pattern widely different from their own, for example, bacterial antigens, but was able to respond to antigens not greatly different, for example, skin homografts.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

SANITATION OF SYDNEY: GOVERNMENT AND GENERAL ORDERS.[1]

Sydney, August 11, 1850.

His Excellency the Governor deeming it expedient and highly necessary for the improvement and adornment of the town of Sydney to enlarge the streets and avenues thereof, for which a party of the military are now employed at work and who are to be paid for their labour out of the Police Fund—The Governer therefore orders and directs that as far as circumstances will permit, the width of the streets shall be fifty feet including a footway on each side: that the paling or palisading on each side shall be of a uniform height of four feet and put up in a neat, regular and durable manner: and he trusts and expects that such persons as have it in their power will voluntarily assist by voluntarily removing back their own palings and inclosures.

[1] From the original in the Mitchell Library, Sydney.

Should any houses stand in the way of the intended improvements which it may be necessary to remove, they will be erected again at the public expense or a fair pecuniary remuneration allowed to the proprietors in case they should prefer it.

His Excellency the Governor further orders and directs that no person whatever shall erect any house or dwelling in the town of Sydney whether on leasehold ground or otherwise without previously obtaining his permission through Mr. Meehan, the acting surveyor, who has a plan of the town recently made out and approved by His Excellency with instructions respecting the several parts thereof which the Governor deems most proper to improve and have uniform buildings erected thereon. A non compliance with these orders will subject the proprietors to have their houses pulled down and further incur the Governor's displeasure. But he trusts the inhabitants whose interests may at first view appear to be affected by these regulations will yield a ready and cheerful obedience to the orders now published on account of the great benefit the public at large will derive from them and the additional convenience and ornament the town will acquire by their being carried into effect.

Whereas horse and foot passengers in the streets of Sydney sustain great inconvenience and danger by pigs, goats and dogs being permitted to wander at large through the town; and very serious injury is done to gardens and inclosures of the inhabitants by pigs and goats breaking through the fences and destroying the productions in said inclosures—This is therefore to give notice that on and after the 18th day of the present month, all persons who keep pigs, goats or dogs are required to confine them within the limits of their own premises, and those who have pigs are required to yoke and ring them so as to prevent their doing such injury in the future. Pigs which may be found in the streets or about the tanks where they dirty or render unfit for use the water collected for the accommodation of the inhabitants will be seized and sold for the benefit of the Orphan Fund and of the persons who make the seizure two thirds of the value to be placed into the hands of the treasurer of the Orphan Fund and the remaining one third to the person who shall seize them. Goats found in the streets or within inclosures will be seized and disposed of in the like manner and distributed in the same proportions and the constables and their assistans are strictly commanded to seize and secure all pigs and goats straying through the streets that they may be disposed of for the beforementioned purposes.

The constables are also required to caution such persons as keep dogs which are in the habit of running at men or horses, either to cause them to be tied up or to destroy them, as in future they will be killed by the constables when found attacking men or horses and the owners fined for disobedience of this public notice and order.

Obituary.

ARCHIBALD CRAIG TELFER.

DR. R. E. MAFFEY writes: I would like to add my tribute to the memory of the late Archibald Craig Telfer. His skill and standing in his beloved specialty of urology was widely recognized by the medical profession and by the public, and though he will be missed in that regard, the man himself is yet a greater loss to his many friends in all walks of life. His personality was one which inspired confidence and trust, and his capacity for understanding and a willingness to help, combined with a wealth of sound common sense, made him the confidant and adviser to many of his friends and patients.

To those who knew him as a resident medical officer at Sydney Hospital, Archie's boundless enthusiasm and tireless energy were always a source of amazement and of inspiration. Whether it was the solving of some obscure clinical problem, or skiing on the sandhills at Long Reef in preparation for his winter holiday at Kosciusko, he did it with the same relentless zeal. The restrictions imposed on him in 1938 by a prolonged and serious illness would be shattering enough for any man, but to Archie, who crammed so much into every minute and enjoyed the doing to the full, it must have been an indescribable calamity. Never in any way did he show that this was so, nor, in later years, when coronary occlusion added its further restriction to his activities, did he ever complain. Cut off from all the forms of sport which he loved, he devoted himself even more to his great interest, the human "waterworks", and turned to less arduous hobbies, such as the study of wildflowers in collaboration with his wife.

Time spent in yarning with Archie Telfer was never wasted—one always went away with some new piece of information, with food for profitable thought. His code of life in general, and of friendship in particular, was of an order that is far too seldom encountered.

Correspondence.

A COLLEGE OF GENERAL PRACTITIONERS.

SIR: At the annual meeting of delegates of Local Medical Associations with the New South Wales Branch Council of the British Medical Association, which was held in Sydney on October 2, 1953, a committee was appointed to take whatever action was deemed necessary for the formation of a College of General Practitioners. This committee consists of Dr. G. N. M. Aitkens (Sydney), Dr. F. P. M. Solling (Maitland), Dr. Colin Warburton (Sydney) and Dr. W. A. Conolly (Cessnock), and has coopted Dr. K. C. T. Rawle (Orange) and Dr. D. W. Lawson (Cessnock).

At a meeting in Sydney on October 30, 1953, it was decided to form a Regional Faculty in New South Wales of the English College of General Practitioners. Dr. Conolly was elected chairman and Dr. Lawson honorary secretary of the provisional committee, and it was decided to invite applications for membership of the Faculty.

A person shall be qualified for admission as a member of the Faculty if he complies with the following conditions:

(A) He is a registered medical practitioner; and

(B) (i) He has been engaged in general practice for a total period of not less than twenty years; or

(ii) He has been engaged in general practice for a total period of not less than five years and has in his application for membership undertaken to receive approved post-graduate instruction for not less than three days or six half-days in each year (or five and a half days or eleven half-days in each alternate year) during his membership or until he shall have been engaged in general practice for twenty years or shall have become the holder of an approved higher medical degree or diploma; or

(iii) He has been engaged in general practice for a total period of not less than five years and is the holder of an approved higher medical degree or diploma.

A person shall be qualified for admission as an associate if he complies with the following conditions:

(A) He is a registered medical practitioner; and

(B) He is or contemplates being engaged in general practice, but has not yet been so engaged for a total period of five years or more.

"General practice" means general medical practice as a principal or as a qualified assistant or *locum tenens* of any such person or as an employed general medical officer (whether in Her Majesty's Forces or otherwise).

An entrance fee of ten guineas (sterling) shall be payable upon admission as a member, and an entrance fee of one guinea (sterling) shall be payable upon admission as an associate.

An annual subscription may be found necessary at a later date, and this matter will be decided by the members of the Faculty at the first annual meeting in 1954.

Some of the objects and functions of the College are as follows:

1. *Headquarters.*—To provide a headquarters organized by general practitioners for general practitioners. Its function must be academic and educational, not political, and must supplement the work of the Universities, the British Medical Association, the Royal Colleges and the post-graduate committees, and not compete with them.

2. *Leadership.*—The College will give a lead to general practice by bringing together family doctors of wide experience and of high ideals to fill the many positions created by the founding of this College.

3. *Undergraduate Teaching.*—The College will assist in the training of undergraduate medical students for general practice. It will endeavour to have experienced general

practitioners appointed to the teaching staff of the universities. Also for undergraduates to attend the surgeries of experienced and approved general practitioners and be instructed in the conduct of general practice.

4. *Post-Graduate Teaching.*—(*a*) To collect information on the needs of those entering general practice—for example, equipment and techniques. (*b*) To improve and clarify many aspects of trainee assistantships. (*c*) To help general practitioners to keep abreast of progress in ideas, knowledge and techniques.

5. *Research by General Practitioners.*—The objects of the Research Committee of the College are to assist general practitioners in research work undertaken in their own practices, either single-handed or in study groups. In addition help will be given, if requested, to existing research organizations in the collection of their material.

6. *Traditions.*—To foster the traditions and ideals of general practice and to improve the quality of general practice.

The first annual general meeting of the College of General Practitioners will be held in British Medical Association House, London, on November 14, 1953. At this meeting a president of the College for 1953-1954 will be elected, and the member proposed is Dr. W. N. Pickles, of Aysgarth, Yorkshire, who will be well remembered by practitioners in Australia who have had the pleasure and privilege of meeting or hearing him lecture in 1951. It would be very difficult to find any general practitioner more eminently suited as President of the College.

A list of Foundation Members of the College of General Practitioners as supplied in the first annual report shows that its membership embraces all parts of the British Isles, Eire, all the States in Australia, New Zealand, Canada, Newfoundland, United States of America, Africa, Malaya, Burma, Borneo, Italy, Bahamas, Pakistan and India.

General practitioners in all parts of Australia may become members of the New South Wales Faculty, but practitioners in each State are strongly urged to form their own Faculty from the beginning. It is hoped in 1954 that Regional Faculties will be formed in all the Australian States and that they will be coordinated to form a Council of the College for Australia.

The committee intends to hold a meeting of members of the New South Wales Regional Faculty at Sydney in the early part of 1954. A central office for the headquarters of this Faculty must be found in Sydney to enable it to function properly.

Nomination forms for membership of the College of General Practitioners may be obtained by writing to the Honorary Secretary, Dr. D. W. Lawson, Main Street, Cessnock, New South Wales, and when completed must be returned to him accompanied by a cheque for £13 2s. 6d. (ten guineas sterling). The College in England will return half the entrance fee to the New South Wales Regional Faculty to help finance its formation.

Yours, etc.,

W. A. CONOLLY,
Chairman, Provisional Committee,
New South Wales Regional Faculty.

Main Street,
Cessnock,
New South Wales.
November 6, 1953.

THE MEDICAL BENEVOLENT ASSOCIATION OF NEW SOUTH WALES.

SIR: May I, once again, ask your readers on behalf of those ill, aged and destitute members of our profession, and their dependants, for a generous donation to our Christmas Appeal for funds. A ready response will do much to lessen the burden of those who, through unforeseen circumstances, find themselves without adequate means of support, and so make their Christmas more hopeful and cheerful than it would otherwise have been.

Yours, etc.,

R. J. WHITEMAN,
President, The Medical Benevolent Association of New South Wales.

143 Macquarie Street,
Sydney,
November 16, 1953.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED OCTOBER 24, 1953.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	5(3)	2	..	..	..	..	..	..	7
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	7	..	..	..	1	..	8
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	1	..	..	1(1)	..	..	..	2
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	1	..	..	..	..	..	..	..	1
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	3(2)	3(2)	7(7)	..	..	..	..	..	13
Diphtheria	2(1)	3(2)	4(1)	..	..	..	..	..	9
Dysentery (Bacillary)	..	..	3(2)	2(1)	..	..	..	..	5
Encephalitis	1	..	..	1(1)	..	..	1	..	3
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	2(1)	..	..	..	1	..	..	3
Infective Hepatitis	..	13(2)	..	..	1(1)	..	..	..	14
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	1	..	..	..	..	..	1
Leptospirosis	..	..	1	..	..	..	..	..	1
Malaria	..	..	..	..	..	2(1)	..	..	2
Meningococcal Infection	..	2(2)	1(1)	..	..	2(2)	..	..	5
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	1(1)	..	..	..	..	..	..	..	1
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	9(5)	1(1)	1	4(2)	..	..	..	..	15
Puerperal Fever	..	..	1	..	..	..	..	..	1
Rubella	..	4(4)	1(1)	..	32(26)	..	..	..	37
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	12(6)	21(11)	20(14)	2	1(1)	..	..	..	56
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	1	2(2)	..	..	..	..	..	3
Trachoma	..	..	..	..	..	..	..	..	..
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	57(45)	31(27)	13(7)	2(2)	12(8)	3(2)	1	2	121
Typhoid Fever	1(1)	1	..	..	1(1)	..	..	..	3
Typhus (Flea-, Mite- and Tick-borne)	..	..	1	..	..	..	..	..	1
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Clinical Meeting at Balmoral Naval Hospital.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that a clinical meeting will be held at the Balmoral Naval Hospital on Tuesday, December 8, 1953, at 2 p.m., when Dr. H. Windsor will speak on "Injuries of the Chest". Clinical cases will be shown after the lecture. All members of the medical profession are invited to attend.

The Royal Australasian College of Physicians.

Admissions to Membership.

THE following candidates, who were successful at an examination for Membership held in September-October, 1953, were admitted to Membership of The Royal Australasian College of Physicians at a meeting of the Council of the College held on October 14, 1953: Dr. John Benecke, Dr. Ralph Blacket, Dr. W. H. Cary, Dr. D. L. Hobson, Dr. J. G. Richards and Dr. Lyal Watson, of New South Wales; Dr. J. W. Bennett, Dr. G. W. Cooper and Dr. P. M. Robertson, of Victoria; Dr. G. L. Bennett, of South Australia; Dr. R. F. O'Shea, of Queensland; Dr. K. S. Millingen and Dr. N. M. Newman, of Tasmania.

Annual Meeting, 1954.

The annual meeting of the College in 1954 will take place at Melbourne from Wednesday, May 26, to Saturday, May 29.

Examination for Membership.

An examination for Membership of The Royal Australasian College of Physicians will be held in April-May, 1954. The written examination will be held on Saturday, April 3, 1954, in capital cities of the Commonwealth where candidates are offering. The clinical examination will be in Melbourne from approximately Friday, May 21, to Tuesday, May 25, 1954. Only those candidates whose answers in the written examination have attained a satisfactory standard will be asked by the Censor-in-Chief to proceed to the clinical examination.

Applications to appear before the Board of Censors should be made in the prescribed form and must be in the hands of the Honorary Secretary of the College not later than Saturday, March 6, 1954. Application forms are obtainable from the Honorary Secretary, 145 Macquarie Street, Sydney.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Harden, William George, 72 Merrigang Street, Bowral, New South Wales.

Bushell, Douglas Ian, 132 Carthage Street, Tamworth, New South Wales.

Bluett, Kenneth Gabriel, 21 South Street, Marrickville, New South Wales.

The undermentioned have been elected as members of the New South Wales Branch of the British Medical Association: Archer, Gordon Thomson, M.B., B.S., 1953 (Univ. Sydney); Jennis, Francis, M.B., B.S., 1953 (Univ. Sydney); O'Connor, Arthur Gerard, M.B., B.S., 1953 (Univ. Sydney); Spragg, Griffith Silas, M.B., B.S., 1953 (Univ. Sydney); Calov, Walter Tom, M.B., B.S., 1952 (Univ. Sydney); Collins, Kenneth Leslie, M.B., B.S., 1952 (Univ. Sydney); Lynch, Gilbert Edward, M.B., B.S., 1948 (Univ. Sydney); Mayne, Stephen Leigh, M.B., B.S., 1952 (Univ. Sydney); Smith, Bruce John, M.B., B.S., 1948 (Univ. Sydney).

Notice.

A CLINICAL MEETING of the Laennec Society will be held in the Students' Common Room, Royal North Shore Hospital of Sydney, on Monday, December 7, 1953, at 8 p.m. Members are invited to bring any guests who may be interested.

Deaths.

THE following deaths have been announced:

DAY.—Frederick Arthur Day, on November 7, 1953, at Regent, Victoria.

MACKNIGHT.—Charles Crawford Macknight, on November 5, 1953, at Melbourne, Victoria.

Diary for the Month.

DEC. 1.—New South Wales Branch, B.M.A.: Organization and Science Committee.
DEC. 2.—Victorian Branch, B.M.A.: Annual Meeting.
DEC. 2.—Victorian Branch, B.M.A.: Branch Council Meeting.
DEC. 2.—Western Australian Branch, B.M.A.: Council Meeting.
DEC. 3.—New South Wales Branch, B.M.A.: Clinical Meeting.
DEC. 7.—Victorian Branch, B.M.A.: Executive of Branch Council.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in the Commonwealth can become subscribers to the journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rate is £5 *per annum* within Australia and the British Commonwealth of Nations, and £6 10s. *per annum* within America and foreign countries, payable in advance.